UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

INFORMED CONSENT ACTION NETWORK, Plaintiff, -against- UNITED STATES FOOD AND DRUG ADMINISTRATION Defendant.	**COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF**

Plaintiff, as for its Complaint against the above-captioned Defendant, alleges as follows:

INTRODUCTION

1. Federal regulations require that "[a]fter a license has been issued" for a biological product by the Food and Drug Administration ("**FDA**"), "data and information in the biological product file are *immediately available for public disclosure* unless extraordinary circumstances are shown." 21 C.F.R. § 601.51(e).

2. The FDA issued a license for the biological product Menveo in 2010 but has not yet disclosed the data and information in the biological product file for this product to the public.

3. The disclosure of this information is a matter of immediate public interest because a leading COVID-19 vaccine being developed by the University of Oxford and AstraZeneca (the "ChAdOx1" or "ChAdOx1 Vaccine") is using Menveo, rather than a placebo, as the control in its clinical trial; and there has been wide and up-to-the minute reporting regarding any development in this clinical trial. Furthermore, the FDA has approved the clinical trial design for the ChAdOx1 Vaccine, and the federal government has poured billions of dollars into AstraZeneca, the company manufacturing and which will sell the ChAdOx1 Vaccine.

4. The data and information underpinning the licensure of Menveo, and in particular its safety profile, is also a matter of urgent public attention because the federal and state governments may soon make ChAdOx1 Vaccine mandatory for many Americans.

5. Plaintiff Informed Consent Action Network ("**Plaintiff**" or "**ICAN**") is a non-profit organization that advocates for informed consent and disseminates information necessary for same with regard to all medical interventions. Given its mission, ICAN and its founder, Del Bigtree, have received many inquiries regarding the ChAdOx1 Vaccine. In particular, since ChAdOx1 Vaccine's safety will be compared to the safety of Menveo, instead of to a saline placebo, there is significant interest in reviewing the clinical trials and safety information for Menveo.

6. In order to gather this safety information for Menveo, plaintiff made an expedited request to the FDA pursuant to the Freedom of Information Act (5 U.S.C. §552, as amended) ("**FOIA**") for the data required to be disclosed under 21 C.F.R. § 601.51(e) regarding Menveo, including "all safety and effectiveness data and information."

7. Ignoring both 21 C.F.R. § 601.51(e) and the manifest compelling need for the documents requested, the FDA denied expedited processing for this request.

8. This FOIA request sought documents that the FDA should have easily and promptly been able to produce, as required by both 21 C.F.R. § 601.51(e) and FOIA. ICAN therefore brings this action seeking an order directing Defendant to expeditiously produce records responsive to ICAN's FOIA request.

PARTIES

9. Plaintiff Informed Consent Action Network is a not-for-profit organization with an office located at 140 Broadway, 46th Floor, New York, New York 10005.

10. Defendant FDA is an agency within the Executive Branch of the United States Government, organized within the Department of Health and Human Services. The FDA is an agency within the meaning of 5 U.S.C. §552(f).

JURISDICTION AND VENUE

11. This Court has jurisdiction over this action pursuant to 5 U.S.C. § 552(a)(4)(B) and 28 U.S.C. § 1331. Venue is proper within this District pursuant to 5 U.S.C. § 552(a)(4)(B) and 28 U.S.C. § 1391(a).

FACTS

12. Menveo is a biological product licensed by the FDA on February 19, 2010.[1]

13. Federal regulations provide that "[t]he availability for public disclosure of any record in a biological product file shall be handled in accordance with the provisions of" 21 C.F.R. § 601.51. That section provides, in relevant part, as follows:

> *After a license has been issued*, the following data and information in the biological product file are *immediately available for public disclosure* unless extraordinary circumstances are shown:
>
> (1) All safety and effectiveness data and information.
> (2) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61 of this chapter.
> (3) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:
>
> > (i) Names and any information that would identify the person using the product.
> > (ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.
>
> (4) A list of all active ingredients and any inactive ingredients previously disclosed to the public, as defined in § 20.81 of this chapter.

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5909a5.htm (last visited July 17, 2020).

> (5) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and it is shown to fall within the exemption established in § 20.61 of this chapter.
> (6) All correspondence and written summaries of oral discussions relating to the biological product file, in accordance with the provisions of part 20 of this chapter.

(emphasis added).

14. ICAN therefore made the following expedited FOIA request to the FDA on June 11, 2020, mirroring the language in 21 C.F.R. § 601.51(e):

> The following data and information in the biological product file for MENVEO:
>
> (1) All safety and efficacy data and information;
> (2) All protocols for a test or study;
> (3) All adverse reaction reports, product experience reports, consumer complaints, and other similar data and information;
> (4) A list of all active ingredients and any inactive ingredients previously disclosed to the public;
> (5) An assay method or other analytical method; and
> (6) All correspondence and written summaries of oral discussions relating to the biological product file.

(**Exhibit A**).[2]

15. Later the same day, the FDA acknowledged receipt of the FOIA request and assigned the request number 2020-4378. (**Exhibit B**).

16. On June 12, 2020, Katherine Uhl, the FDA Denials and Appeal Officer, sent an email attaching a letter from Sarah B. Kotler, Director, which stated in relevant part:

> This is in reference to your request(s) for record(s) from the Food and Drug Administration (FDA) pursuant to the Freedom of Information Act (FOIA).
>
> The [request was for the] following data and information in the biological product file for MENVEO: (1) All safety and efficacy data and information; (2) All protocols for a test or study; (3) All adverse reaction reports, product experience reports, consumer

[2] All "Exhibits" referenced herein are appended to this pleading.

> complaints, and other similar data and information; (4) A list of all active ingredients and any inactive ingredients previously disclosed to the public; (5) An assay method or other analytical method; and (6) All correspondence and written summaries of oral discussions relating to the biological product file.
>
> The Electronic Freedom of Information Act (EFOIA) Amendments of 1996 amended the FOIA by adding section (a)(6)(E), 5 U.S.C. 552(a)(6)(E), to require agencies to consider requests for expedited processing and grant them whenever a "compelling need" is shown and in other cases as determined by the agency. The term "compelling need" is defined as (1) involving "an imminent threat to the life or physical safety of an individual," or (2) in the case of a request made by "a person primarily engaged in disseminating information, urgency to inform the public concerning actual or alleged Federal Government activity."
>
> I have determined that your request for expedited processing does not meet the criteria under the FOIA. *You have not demonstrated a compelling need that involves an imminent threat to the life or physical safety of an individual. Neither have you demonstrated that there exists an urgency to inform the public concerning actual or alleged Federal Government activity*. Therefore, I am denying your request for expedited processing. The responding agency office will process your request in the order in which it was received.

(**Exhibit C**) (emphasis added).

17. Based on 21 C.F.R. § 601.51(e), obtaining the data requested by Plaintiff should not even require an expedited FOIA request because, absent "extraordinary circumstances," this data should have been "immediately available for public disclosure." 21 C.F.R. § 601.51. The FDA nonetheless disregarded this obligation and stated, without explanation, that there is no "urgency to inform the public concerning actual or alleged Federal Government activity." To the contrary, the requested data is being made by "a person primarily engaged in disseminating information" and there is clear "urgency to inform the public concerning actual or alleged Federal Government activity" regarding the licensure of Menveo, including because Menveo was licensed

by the federal government and the development and production of ChAdOx1, which is being safety tested against Menveo, is being funded by the federal government.

18. One of the leading vaccines for COVID-19 to begin trials in the United Kingdom (and very soon in the United States) is the ChAdOx1 Vaccine being developed by Oxford University and AstraZeneca.

19. Information regarding this vaccine, and in particular the safety and efficacy information, are a matter of immediate concern to the American public, especially given the extensive media and public interest in the fate of the clinical trials for preventing this virus.[3] As Oxford University has publicly explained, its "study aims to assess how well people across a broad range of ages could be protected from COVID-19 with this new vaccine called ChAdOx1. It will also provide *valuable information on safety aspects of the vaccine* and its ability to generate good immune responses against the virus."[4]

20. News outlets have widely reported about this vaccine, its clinical trials and potential timing of availability, which provides additional grounds for rendering the information requested a matter of immediate attention and concern to the American public.[5] "AstraZeneca has [also] received more than $1 billion from the U.S. Health Department's Biomedical Advanced Research and Development Authority to develop a coronavirus vaccine from the University of

[3] *See, e.g.*, https://www.nih.gov/news-events/news-releases/investigational-chadox1-ncov-19-vaccine-protects-monkeys-against-covid-19-pneumonia; https://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials; https://www.cnbc.com/2020/05/21/coronavirus-us-gives-astrazenena-1-billion-for-oxford-vaccine.html; https://www.cnbc.com/2020/06/04/astrazeneca-is-set-to-make-two-billion-doses-of-a-coronavirus-vaccine.html (last visited July 17, 2020).

[4] http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials (emphasis added) (last visited July 17, 2020).

[5] *See, e.g.*, https://www.nih.gov/news-events/news-releases/investigational-chadox1-ncov-19-vaccine-protects-monkeys-against-covid-19-pneumonia; https://www.cnbc.com/2020/06/04/astrazeneca-is-set-to-make-two-billion-doses-of-a-coronavirus-vaccine.html (last visited July 17, 2020).

Oxford."[6] This funding is being used to start producing this vaccine, even prior to licensure, with reports explaining that AstraZeneca "has agreed to initially supply at least 400 million doses of the vaccine…with first deliveries in September."[7]

21. The study design for the Phase I/II clinical trial of the ChAdOx1 Vaccine initially provided that the control group in this clinical trial would receive a "Saline Placebo."[8] After approving this study design, the FDA inexplicably approved a change of the control from a "Saline Placebo" to "MenACWY."[9] In the United States, the brand name for the MenACWY vaccine is Menveo.[10] The Phase II/III clinical trial for the ChAdOx1 Vaccine similarly provides that the control group will receive the MenACWY vaccine.[11]

22. According to the Centers for Disease Control & Prevention and the FDA, randomized placebo-controlled trials are the standard for determining the safety and efficacy of a new drug or biological product, including new vaccines. A "placebo" is defined as "[a] substance or treatment that has no effect on human beings."[12] Clinical trials for new pharmaceutical products typically do not use a non-inert substance as a control – which is precisely what is happening with ChAdOx1 – because, due to its pharmacological effects, a non-inert substance makes it impossible to isolate the effects of just the experimental product being studied.[13]

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[6] https://www.cnbc.com/2020/05/21/coronavirus-us-gives-astrazenena-1-billion-for-oxford-vaccine.html (last visited July 17, 2020).

[7] https://www.cnbc.com/2020/05/21/coronavirus-us-gives-astrazenena-1-billion-for-oxford-vaccine.html (last visited July 17, 2020).

[8] https://clinicaltrials.gov/ct2/history/NCT04324606 (last visited July 17, 2020).

[9] https://clinicaltrials.gov/ct2/history/NCT04324606?A=1&B=2&C=merged#StudyPageTop

[10] https://www.cdc.gov/vaccines/terms/usvaccines.html (last visited July 17, 2020).

[11] https://clinicaltrials.gov/ct2/show/NCT04400838?term=ChAdOx1+nCoV-19&draw=2&rank=2

[12] https://www.cdc.gov/vaccines/terms/glossary.html (last visited July 17, 2020).

[13] Reflecting the central role of placebos in testing, on May 24, 2020, a member of the FDA's Vaccines and Related Biological Products Advisory Committee, Dr. Paul Offit, told CNN News that, in order to

23. COVID-19 primarily effects the elderly and the National Institute of Aging, an institute within the National Institutes of Health, has likewise explained that:

> In undertaking a clinical trial, researchers don't want to leave anything to chance. They want to be as certain as possible that the results of the testing show whether or not a treatment is safe and effective. The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial. ... A placebo is an inactive substance.[14]

24. Where an effective vaccine already exists for an infection, ethical considerations may require using the existing vaccine, rather than a placebo, as the control (an "**active control**"). The FDA's industry guidance explains that an "active control must be a drug whose effect is well defined," which means "historical placebo-controlled trials are available to define the active control effect."[15] The importance of only using an active control that has already been licensed based on a placebo-controlled trial is explained by the FDA as follows:

> The placebo-controlled trial measures the total pharmacologically mediated effect of treatment. In contrast, an active control trial … measures the effect relative to another treatment. The placebo-controlled trial also allows a distinction between adverse events due to the drug and those due to the underlying disease or background noise.[16]

25. Because there is no licensed COVID-19 vaccine, an active control is not appropriate for trials of new COVID-19 vaccines. This is precisely why the FDA, in its guidance entitled *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry*, published

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determine whether a COVID-19 vaccine is safe and effective, "we are waiting for the big trial… the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a placebo, then and only then will you know whether a vaccine is safe and effective." https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn (emphasis added) (last visited July 17, 2020).

[14] https://www.nia.nih.gov/health/why-are-placebos-important (last visited July 17, 2020).

[15] https://www.fda.gov/media/78504/download (last visited July 17, 2020).

[16] *Id.*

on June 30, 2020, expressly provides that "[l]ater phase trials [for COVID-19 vaccines], including efficacy trials, should be randomized, double-blinded, and **placebo** controlled."[17]

26. Thus, where Menveo is being used as the active control, in contradiction to the FDA's standards, understanding the full safety and efficacy profile of Menveo is critical for understanding the safety and efficacy profile of ChAdOx1. This need is made more acute by the fact that Menveo was not licensed based on a placebo-controlled clinical trial.[18]

27. It is therefore imperative that the public and scientific community have full access to the safety information regarding the active control, Menveo, being used in the clinical trial to license ChAdOx1. It is public knowledge that, "[t]o date AstraZeneca has concluded agreements for at least 400 million doses and secured total manufacturing capacity for 1bn billion doses of the Oxford vaccine."[19] This shows the impending nature of widespread use of this vaccine which is intended to be administered to most Americans, either voluntarily or by compulsion, with the first doses "anticipated to be available in early 2021."[20]

28. Judicial scholars have already begun to opine regarding the legality of mandating any potential COVID-19 vaccine to all adults. Alan Dershowitz, for example, recently stated that

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[17] https://www.fda.gov/media/139638/download (emphasis added)

[18] *Id*. The trade name for MenACWY vaccine in the United States is Menveo. This product was licensed for adults based on a clinical trial in which the control group of 1,966 participants received either Menomune (209 participants) or Menactra (1,757 participants). https://www.fda.gov/media/78514/download (last visited July 17, 2020). Menactra was licensed based on a clinical trial in which Menomune was the active comparator. https://www.fda.gov/media/75619/download (last visited July 17, 2020). Quizzically, the clinical trials section of the package insert for Menomune only lists the clinical trial in which it was used as a comparator against Menactra. https://www.fda.gov/media/83562/download (last visited July 17, 2020). Meaning, the same clinical trial in which Menactra was studied with Menomune as its active control is apparently relied upon by the FDA to support the safety of both of these products. Using any of these products as an active control for a COVID-19 vaccine is unscientific and unacceptable. The control should be a saline placebo.

[19] https://www.ox.ac.uk/news/2020-06-04-brazilian-health-regulatory-agency-approves-trial-oxford-covid-19-vaccine (last visited July 17, 2020).

[20] https://www.precisionvaccinations.com/vaccines/azd1222-sars-cov-2-vaccine (last visited July 17, 2020).

he would support such a mandate, adding that, "if you refuse to be vaccinated, the state has the power to literally take you to a doctor's office and plunge a needle into your arm."[21] Mr. Dershowitz appeared on ICAN's public broadcast, The HighWire with Del Bigtree, to defend this position, including specifically addressing mandating a COVID-19 vaccine for adults.[22]

29. Moreover, states are expected to mandate the vaccine for all their residents. For example, the New York State Bar Association recently issued a report on COVID-19 recommending that, "[w]hen the efficacy of a COVID-19 vaccine has been confirmed" states should "enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate."[23] The FDA's parent department has also granted those developing and those who will sell this product broad immunity from liability for injuries.[24] The result could be a product whose administration is required by compulsion of law, where the recipient of the product cannot sue the manufacturer for injury.

30. Given (i) the right to immediate public disclosure of this data under applicable Federal regulations, (ii) the public interest in potential COVID-19 vaccines and their clinical trials, and (iii) the potential for states to mandate its use by nearly all citizens, which is antithetical to informed consent, ICAN submitted its FOIA request to the FDA.

31. The FDA has failed to abide by its duty pursuant to 21 C.F.R. § 601.51 and has failed to recognize the compelling need for this data, forcing ICAN to come before this Court to seek an order directing the FDA to grant expedited processing and production of Plaintiff's FOIA

[21] https://youtu.be/tuoM3QGSUhM (last visited July 17, 2020).

[22] *Id*.

[23] https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited July 17, 2020).

[24] https://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx (last visited July 17, 2020).

request. The information ICAN seeks is simply too important to the current public discourse regarding the COVID-19 pandemic to allow the FDA to hide or delay such information from public scrutiny.

REQUESTED RELIEF

WHEREFORE, Plaintiff prays that this Court:

a. Provide for expeditious proceedings in this action;

b. Enter an Order declaring that it was unlawful for the FDA to fail to grant expedited processing;

c. Enter an Order directing the FDA to, within 5 days, provide the requested information and data in Plaintiff's FOIA request;

d. Award Plaintiff its costs and reasonable attorneys' fees incurred in this action as provided by 5 U.S.C. § 552(a)(4)(E); and

e. Grant such other and further relief as the Court may deem just and proper.

Dated: July 17, 2020

SIRI & GLIMSTAD LLP

Aaron Siri
Elizabeth A. Brehm
200 Park Avenue, 17th Floor
New York, New York 10166
Tel: (212) 532-1091
Counsel for Plaintiff

Exhibit A

Siri | Glimstad

200 Park Avenue, Seventeenth Floor, New York, NY 10166
sirillp.com | P: (212) 532-1091 | F: (646) 417-5967

FREEDOM OF INFORMATION ACT REQUEST

REQUEST FOR EXPEDITED PROCESSING

VIA EMAIL June 11, 2020

Food and Drug Administration
Division of Freedom of Information
Office of the Secretariat, OC
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Re: *Safety & Efficacy Data for MENVEO (IR#0305)*

Dear Sir or Madam:

This firm represents the Informed Consent Action Network ("ICAN"). On behalf of ICAN, please provide the following records to foia@sirillp.com in electronic form:

The following data and information in the biological product file for MENVEO:

(1) All safety and efficacy data and information;
(2) All protocols for a test or study;
(3) All adverse reaction reports, product experience reports, consumer complaints, and other similar data and information;
(4) A list of all active ingredients and any inactive ingredients previously disclosed to the public;
(5) An assay method or other analytical method; and
(6) All correspondence and written summaries of oral discussions relating to the biological product file.

Request For Expedited Processing

ICAN requests expedited processing for this request. ICAN is "primarily engaged in disseminating information to the general public" and there is an "urgency to inform the public concerning actual or alleged Federal Government activity." 5 U.S.C. § 552(a)(6)(E)(v)(II).

Specifically, ICAN's mission is to raise public awareness about public health safety and to provide the public with information to give informed consent regarding related health interventions. ChAdOx1 nCoV-19 is a leading experimental vaccine against novel coronavirus, SARS-CoV-2, also known as COVID-19. Information regarding this vaccine, and in particular the safety and efficacy information regarding this vaccine, are a matter of immediate concern to the American public, given the extensive media and public interest in the fate of the clinical trials for preventing this virus. *See, e.g.,* https://www.nih.gov/news-events/news-releases/investigational-chadox1-ncov-19-vaccine-protects-monkeys-against-covid-19-pneumonia; http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials; https://www.cnbc.com/2020/05/21/coronavirus-us-gives-astrazenena-1-billion-for-oxford-vaccine.html; https://www.cnbc.com/2020/06/04/astrazeneca-is-set-to-make-two-billion-doses-of-a-coronavirus-vaccine.html

It has been made public by University of Oxford, the sponsor for the clinical trial for ChAdOx1 nCoV-19, and by AstraZeneca, its developer, that MENVEO will be used as a "control" in its Phase II and Phase III trials of ChAdOx1 nCoV-19. *See* http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials.; https://clinicaltrials.gov/ct2/show/NCT04400838?term=ChAdOx1+nCoV-19&draw=2&rank=1. The licensure and safety information regarding MENVEO requested herein are therefore of immediate concern to the American public. It is imperative that the public have full access to the safety information regarding the active control, MENVEO, being used in the clinical trial to license the COVID vaccine, ChAdOx1 nCoV-19, including because this vaccine is intended to be administered to most Americans, either voluntarily or by compulsion. *See, e.g.,* https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited June 2, 2020) (The New York State Bar Association report on COVID-19 recommending that "[w]hen the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate."); https://youtu.be/tuoM3QGSUhM (Constitutional Scholar and Harvard Law Professor Alan Dershowitz stating that he would support mandating a COVID-19 vaccine and that "if you refuse to be vaccinated, the state has the power to literally take you to a doctor's office and plunge a needle into your arm.")

Moreover, news articles have widely reported about the above vaccine and its clinical trials which provide an additional ground for rendering the information requested above a matter of immediate attention and concern to the American public. *See, e.g.,* https://www.nih.gov/news-events/news-releases/investigational-chadox1-ncov-19-vaccine-protects-monkeys-against-covid-19-pneumonia; http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials; https://www.cnbc.com/2020/05/21/coronavirus-us-gives-astrazenena-1-billion-for-oxford-vaccine.html; https://www.cnbc.com/2020/06/04/astrazeneca-is-set-to-make-two-billion-doses-of-a-coronavirus-vaccine.html

ICAN certifies that the information in the request is true and correct to the best of ICAN's knowledge and belief.

Fees and charges for this search are to be waived pursuant to 5 U.S.C. § 552 (a)(4)(A)(iii) since ICAN is a not-for-profit 501(c)(3) organization and its mission is to raise public awareness about public health safety and provide the public with information to give informed consent

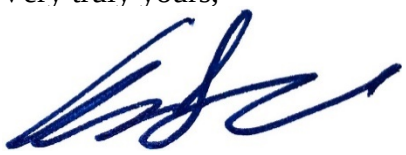
regarding related health interventions. As part of its mission, ICAN investigates and disseminates information regarding public health safety issues, including through their website, and through press events and releases. ICAN is seeking the information in this FOIA request to allow it to contribute to its mission. The information requested in this FOIA request will not contribute to any commercial activities.

Please note that the FOIA provides that if only portions of a requested file are exempted from release, the remainder must still be released. We, therefore, request that we be provided with all non-exempt portions which are reasonably segregable. We further request that you describe any deleted or withheld material in detail and specify the statutory basis for the denial as well as your reasons for believing that the alleged statutory justification applies. Please also separately state your reasons for not invoking your discretionary powers to release the requested documents in the public interest. Such statements may help to avoid unnecessary appeal and litigation. ICAN of course reserves all rights to appeal the withholding or deletion of any information.

Access to the requested records should be granted within, at most, twenty (20) business days from the date of your receipt of this letter. Failure to respond in a timely manner shall be viewed as a denial of this request and ICAN may immediately file an administrative appeal.

If you would like to discuss our requests or any issues raised in this letter, please feel free to contact me at (212) 532-1091 or via email at foia@sirillp.com during normal business hours. Thank you for your time and attention to this matter.

Very truly yours,



Aaron Siri, Esq.

Exhibit B

Subject: FDA Receipt of FOI Request
Date: Thursday, June 11, 2020 at 1:57:59 PM Pacific Daylight Time
From: FDA_FOI@fda.gov
To: S&G Information Request Staff

Informed Consent Action Network Informed Consent Action Network

Re: Confirmation # FDA2065541
Requester Ctrl #:
In Reply refer to: 2020-4378

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

The following data and information in the biological product file for MENVEO: (1) All safety and efficacy data and information; (2) All protocols for a test or study; (3) All adverse reaction reports, product experience reports, consumer complaints, and other similar data and information; (4) A list of all active ingredients and any inactive ingredients previously disclosed to the public; (5) An assay method or other analytical method; and (6) All correspondence and written summaries of oral discussions relating to the biological product file.

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm.

Due to an increase in the number of incoming requests, we may be unable to comply with the twenty-working-day time limit in this case, as well as the ten additional days provided by the FOIA. The actual processing time will depend on the complexity of your request and whether sensitive records, voluminous records, extensive search, and/or consultation with other HHS components or other executive branch agencies are involved. Please note that requests for medical device approval records (e.g. 510K, PMA, DEN) may take up to 18 to 24 months to process.

If you have any questions about your request, please call Rochelle A. Coleman, Information Technician at 301-796-8982 or write to us at:

Division of Freedom of Information,
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
Fax: 301-827-9267

You also have the right to seek dispute resolution services from:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-Mail: FDAFOIA@fda.hhs.gov

and/or:

Office of Government
Information Services
National Archives and Administration
8601 Adelphi Road - OGIS
College Park, MD 20740-6001

College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-Mail: ogis@nara.gov
Fax: 202-741-5769

Note: Do NOT reply directly to this E-mail

Exhibit C

U.S. FOOD & DRUG ADMINISTRATION

June 12, 2020

INFORMED CONSENT ACTION NETWORK
INFORMED CONSENT ACTION NETWORK
10200 US HWY 290 W
Suite 301
Austin TX 78736 US

In Reply refer to:

2020-4378

Requester Control #:

Dear Requester:

This is in reference to your request(s) for record(s) from the Food and Drug Administration (FDA) pursuant to the Freedom of Information Act (FOIA).

The following data and information in the biological product file for MENVEO: (1) All safety and efficacy data and information; (2) All protocols for a test or study; (3) All adverse reaction reports, product experience reports, consumer complaints, and other similar data and information; (4) A list of all active ingredients and any inactive ingredients previously disclosed to the public; (5) An assay method or other analytical method; and (6) All correspondence and written summaries of oral discussions relating to the biological product file.
The Electronic Freedom of Information Act (EFOIA) Amendments of 1996 amended the FOIA by adding section (a)(6)(E), 5 U.S.C. 552(a)(6)(E), to require agencies to consider requests for expedited processing and grant them whenever a "compelling need" is shown and in other cases as determined by the agency. The term "compelling need" is defined as (1) involving "an imminent threat to the life or physical safety of an individual," or (2) in the case of a request made by "a person primarily engaged in disseminating information, urgency to inform the public concerning actual or alleged Federal Government activity."

I have determined that your request for expedited processing does not meet the criteria under the FOIA. You have not demonstrated a compelling need that involves an imminent threat to the life or physical safety of an individual. Neither have you demonstrated that there exists an urgency to inform the public concerning actual or alleged Federal Government activity. Therefore, I am denying your request for expedited processing. The responding agency office will process your request in the order in which it was received.

You have the right to appeal this determination. Your appeal must be mailed within 90 days from the date of this response, to: Agency Chief FOIA Officer, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Public Affairs, Room 729H, 200 Independence Avenue, S.W., Washington, DC 20201; e-mail FOIARequest@PSC.hhs.gov. Please clearly mark both the envelope and your letter or email “FDA Freedom of Information Act Appeal.”

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact this office at: DFOI, 5630 Fishers Lane, Room 1035, Rockville, MD 20857, 301-796-3900, FDAFOIA@fda.hhs.gov.

You may also contact the FDA FOIA Public Liaison, Office of the Executive Secretariat, 5630 Fishers Lane, Room 1050, Rockville, MD 20857; email: FDAFOIA@fda.hhs.gov.

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman’s office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road–OGIS, College Park, MD 20740-6001, Telephone: 202-741-5770, Toll-Free: 1-877-684-6448, E-mail: ogis@nara.gov, Fax: 202-741-5769.

Sincerely Yours,

Sarah B. Kotler -S

Digitally signed by Sarah B. Kotler -S
Date: 2020.06.12 10:03:05 -04'00'

SARAH KOTLER
Director

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

INFORMED CONSENT ACTION NETWORK, Plaintiffs, -against- UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendant.	**STIPULATION & ORDER** 1:20-cv-05554 (JPO)

WHEREAS, federal regulations require that "[a]fter a license has been issued" for a biological product by the Food and Drug Administration ("**FDA**"), certain "data and information in the biological product file are immediately available for public disclosure unless extraordinary circumstances are shown." 21 C.F.R. § 601.51(e);

WHEREAS, the FDA issued a license for the biological product Menveo on February 19, 2010;[1]

WHEREAS, ICAN sought the clinical trial information for Menveo since ICAN understood it was being used as a control in the clinical trial for the AstraZeneca COVID-19 vaccine and, therefore, made the following expedited FOIA request to the FDA on June 11, 2020, mirroring the language in 21 C.F.R. § 601.51(e):

> The following data and information in the biological product file for MENVEO:
>
> (1) All safety and efficacy data and information;
> (2) All protocols for a test or study;
> (3) All adverse reaction reports, product experience reports, consumer complaints, and other similar data and information;
> (4) A list of all active ingredients and any inactive ingredients

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5909a5.htm (last visited April 14, 2021).

previously disclosed to the public;
(5) An assay method or other analytical method; and
(6) All correspondence and written summaries of oral discussions relating to the biological product file.

WHEREAS, on June 12, 2020, the FDA denied ICAN's request for expedited processing;

WHEREAS, on July 17, 2020, ICAN commenced a lawsuit in the United States District Court, Southern District of New York against the FDA demanding that it produce the documents responsive to the foregoing FOIA Request;

WHEREAS, in the interests of resolving the litigation, ICAN narrowed its requests and the FDA produced the following documents on or before the respective dates:

(1) **September 16, 2020:** Integrated Summary of Clinical Safety (ISS) dated 11 July 2008. **September 30, 2020:** the ISS-associated tables.
(2) **September 30, 2020:** the "License Action Recommendation Documents" requested by ICAN.
(3) **October 14, 2020:** available synopses for studies identified by ICAN.
(4) **October 14, 2020:** available synopses for each of the amendments to STN 125300/0 for which FDA previously provided details.
(5) **October 30, 2020:** PAERs, without appendices, submitted for STN 125300.
(6) **January 27, 2021:** Clinical trial protocols for V59P13, V59P17, V59P18, V59P6, and V59P11.

IT IS HEREBY STIPULATED AND AGREED, by and between the parties by and through their respective counsel that:

1. Pursuant to the FDA's representations that (a) the foregoing constitutes the complete universe of responsive documents as agreed upon by the parties (b) discovered after an adequate search, the above-captioned action is voluntarily dismissed, with prejudice pursuant to Federal Rule of Civil Procedure 41(a)(1)(A)(ii), each side to bear its own costs, attorneys' fees, and expenses;

2. ICAN reserves all rights to seek additional documents, whether or not related to this request, through pending or future FOIA requests to the FDA or any other governmental agency as appropriate and nothing herein shall restrict such right; and

3. This stipulation may be signed in counterparts and electronic (PDF) or fax signatures may be deemed originals for all purposes.

Dated: April 16, 2021
New York, New York

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SO ORDERED:

J. PAUL OETKEN
United States District Judge

Dated: New York, New York
April 19, 2021

5.3.5.3.2 Integrated Summary of Clinical Safety (ISS)

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Glossary Of Terms, Abbreviations, and Definitions

ACA	Anterior Coronary Artery
AE	Adverse Event
B-HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
CBER	Center for Biologics Evaluation And Research
CHMP	Committee for Medicinal Products For Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical Study Report
CT	Computed Tomography
ED	Emergency Department
EEG	Electroencephalogram
ER	Emergency Room / Department
EU	European Union
FCC	Flu Cell Culture
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
GSK	GlaxoSmithKline
HA	Hemagglutinin
HPV	Human Papilloma Virus
ICH	International Conference on Harmonisation
ILI	Influenza-like Illness

IM	Intramuscular
ISS	Integrated Summary of Safety
ITP	Idiopathic Thrombocytopenic Purpura
IVIG	Intravenous Immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
P	Proportion
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	MedDRA System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Supraventricular Tachycardia
Tdap	Tetanus, Diphtheria, and Pertussis
URI	Upper Respiratory Infection
UTI	Urinary Tract Infection
US	United States

Adverse event (AE) = Unsolicited adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An adverse event can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The term "unsolicited" is synonymous with "spontaneously reported by the subject or observed by study staff."

Study day: Study day refers to the number of days after first vaccination, where day of vaccination is day 1.

Solicited AEs (local and systemic reactions): Selected local and systemic AEs are routinely monitored in vaccine clinical studies as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within 7 days after vaccination are herein termed solicited AEs.

Serious adverse event (SAE): These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital anomaly or birth defect, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate medical judgment, may jeopardize the subject. Vaccine failure is also considered an SAE.

Overview of Safety

The safety profile of a single dose of the final formulation of MenACWY meningococcal vaccine (nonadjuvanted MenACWY containing A, C, W-135, and Y antigens in doses of 10 µg, 5 µg, 5 µg, and 5 µg, respectively) was evaluated in 3579 adolescents aged 11 to 18 years and 2606 adults aged 19 to 55 years in three pivotal studies (V59P13, V59P17, and V59P18) and in two supportive studies (V59P6 [adolescents 11 to 17 years of age] and V59P11 [adolescents and adults 11 to 25 years of age]) (Module 5, section 5.2).

In addition to the safety data presented, SAEs are provided for studies in which subjects were outside the 11 to 55 year range and/or administered MenACWY formulations that were studied for dose-, antigen-, and/or adjuvant-selection purposes. In the following studies, single or multiple doses of final or nonfinal MenACWY formulations were administered to subjects in the following age groups: V59P1 (18 to 45 year adults), V59P2 (12 to 16 month toddlers), V59P3 (18 to 45 year adults), V59P4 (12 to 16 month toddlers), V59P5 (2 month infants), V59P7 (12 to 35 month toddlers and 36 to 59 month children], V59P8 (2 to 10 year children and 12 to 23 month toddlers), V59P9 (6 to 12 month infants), V59P10 (2 to 10 year children), ongoing study V59P14 (2 month infants), ongoing study V59P16 (2 month infants), and ongoing study V59P18 (11 to 18 year adolescents; follow-up after day 61 [visit 3]).

For the three ongoing studies (V59P14, V59P16, and V59P18 [follow-up after day 61]), SAEs based on the safety database as of February 15, 2008, are listed and evaluated.

Overview of Pertinent Results

The overall incidence of solicited reactogenic events was similar between groups that received MenACWY (either alone or with a concomitant vaccine) and those that received Menactra. Across all studies, there was a marginally higher percentage of Menactra subjects with at least one solicited local reaction compared with MenACWY subjects, but, conversely, there was a marginally higher percentage of MenACWY subjects with a systemic reaction when compared with Menactra. The majority of events occurred during the first 3 days after vaccination. The percentage of subjects with each type of reaction differed by only 1% to 2% between the two vaccine groups with the exception of injection site pain, for which 5% more Menactra subjects than MenACWY subjects reported pain. The overall rate of any severe solicited local or systemic reaction within the first 7 days after vaccination was similar between the MenACWY and Menactra vaccine groups (8% vs 6%).

Of note, overall reactogenicity after MenACWY given alone was lower than after Tdap alone (any solicited AE was reported in 69% and 82% for MenACWY and Tdap, respectively, and any local reaction was reported in 52% and 74% for MenACWY and Tdap, respectively).

There was some evidence to suggest that reactogenicity was lower in the subjects aged 35 to 55 years; the percentage of subjects reporting at least one solicited AE in MenACWY subjects was 67%, 65%, and 56% for 11 to 18 year-old, 19 to 34 year-old, and 35 to 55 year-old age groups, respectively.

In the examination of the effect of concomitant Tetanus, Diphtheria, and acellular Pertussis (Tdap) and Human Papilloma Virus (HPV) vaccine with MenACWY vaccination, the incidence of systemic reactogenic events was, as expected, slightly higher than when MenACWY was given alone. However, the administration of Tdap vaccination 1 month before MenACWY vaccination did not change the incidence or severity of reactogenic events after MenACWY. MenACWY given after Tdap was comparable to MenACWY given alone.

During month 1 after vaccination, unsolicited AEs were reported in approximately the same percentage of MenACWY and Menactra subjects (17% and 20%, respectively), and only 1% of subjects in each group had unsolicited AEs considered severe. The only unsolicited AE reported in more than 1% of subjects during month 1 postvaccination was headache (2% in each vaccine group). In total, 6% of MenACWY subjects and 7% of Menactra subjects reported unsolicited AEs assessed as possibly or probably related to the vaccine within month 1 postvaccination; most of these started within days 1 to 7 postvaccination.

Similarly, during months 2 to 6 after vaccination, unsolicited AEs were reported in 8% of MenACWY subjects and 9% of Menactra subjects; unsolicited AEs of severe grade were reported by 1% of each group during this time period. Unsolicited AEs assessed as possibly or probably related to the study vaccine were reported by less than 1% of subjects during months 2 to 6, and none were categorized as severe.

Only 1% of subjects had a serious adverse event (an SAE) at any time during the studies in both the MenACWY and Menactra groups. Less than 1% of subjects had an SAE during month 1; SAEs during months 2 to 6 occurred at an incidence of 1% or less. In subjects 11 to 55 years of age, a single SAE was noted as possibly related to vaccine: spontaneous abortion that occurred in one subject on day 44 in study V59P17. The event was considered possibly related to the vaccine because of temporal association without other evidence of causality.

Based on the data from these studies, it is possible to conclude the following:

- The local reactogenicity profile of MenACWY was acceptable and comparable to Menactra;
- MenACWY local reactogenicity was not impacted when given with or after other routinely administered vaccines (i.e., Tdap);
- Systemic reactions were generally mild and of short duration, similar to other licensed vaccines, and usually began within 3 days after vaccination;

- Most unsolicited AEs were considered unrelated to study vaccine. The types of events and their frequencies were similar in the MenACWY and comparator groups

1 Exposure to the Drug

1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

1.1.1 Preclinical Background

In nonclinical studies, MenACWY was immunogenic (mice and rabbits), well tolerated locally and systemically (rabbits), and was not associated with reproductive or developmental toxicity (rabbits). There are no special considerations or observations concerning the nonclinical data (Module 2, section 2.6).

Preclinical experience consisted of immunogenicity studies conducted in mice (including evaluation of formulations with and without adjuvants, monovalent versus tetravalent combinations), and immunogenicity and safety studies conducted in rabbits in the context of single- and multiple-vaccination toxicity and reproduction and developmental toxicity studies.

A toxicity study in rabbits showed that one or five multiple administrations of the Novartis MenACWY formulations were well tolerated. Slight inflammatory changes at the injection sites were the only findings seen microscopically; they partially or fully resolved during the 14-day recovery period.

In an antigen dose-range-finding, pilot reproductive and developmental toxicity study, female rabbits received a total of five intramuscular (IM) MenACWY doses with or without alum; results showed that the vaccine was not maternally toxic or teratogenic, and no embryofetal alterations related to the test article or elicited antibodies were identified.

A definitive reproduction and embryofetal development study in rabbits showed that MenACWY was not maternally toxic or teratogenic and had no effects on postnatal development at the clinical dose administered five times during the course of the study.

1.1.2 Clinical Background and Trial Design

The Novartis quadravalent meningococcal conjugate vaccine (MenACWY) is intended to prevent disease due to *Neisseria meningitidis* serogroups A, C, W-135 (W), and Y. The requested initial indication is for adolescents and adults between the ages of 11 to 55 years, in whom safety was assessed primarily in controlled pivotal studies V59P13, V59P17, and V59P18 and in supportive studies (V59P6 and V59P11) (please refer to CSRs V59P13, V59P17, V59P18, V59P6, and V59P11). Control vaccines were also utilized in these studies, and included vaccines containing polysaccharides of serogroups A, C, W, and Y (Menactra™, Sanofi Aventis; Menomune™, Aventis Pasteur); Tdap, (Boostrix™ [European Union {EU}formulation in V59P11 and US formulation in V59P18]; and HPV (GARDASIL™, Merck).

Safety data from the studies for the proposed indication in the 11 to 55 year age group (V59P6, V59P11, V59P13, V59P17, and V59P18) are provided in this application. SAEs reported through February 15, 2008, are included for all other studies listed.

Safety was assessed in both adolescent (11 to 18 years of age) and adult (19 to 55 years of age) subjects in V59P13. V59P17 enrolled only adults 19 to 55 years of age and adults 56 to 65 years of age. Studies V59P6 and V59P18 enrolled adolescent subjects 11 to 18 years of age. Study V59P11 enrolled adolescent and adult subjects 11 to 25 years of age. Only SAEs for adults aged 56 to 65 years are included in this application.

The five studies (V59P6, V59P11, V59P13, V59P17, and V59P18) were pooled to provide an overall profile of MenACWY safety versus the main comparator vaccine, Menactra. Pooling studies normally enables a powerful safety overview but, in this instance, caused some artificial demographic imbalances due to the varying study designs and study locations. Within each study, demographic characteristics were well balanced between MenACWY and its comparators. Except for ethnicity, the same was true for the pooled adult population, because the designs of studies V59P13 and V59P17 were similar. However, the adolescent study pooling was more problematic because the four studies in adolescents had very different objectives, designs, and geographic location. For this reason, the reactogenicity profile of MenACWY will be discussed with respect to within-study comparisons and, to the extent possible, with respect to across-study comparisons. For the more infrequent unsolicited AEs, the across study pooled data was examined.

The design of all studies for evaluation of safety followed general guidelines as described in Module 5, section 5.3.5.

A tabular listing of all studies in the MenACWY development plan, including regions, subject ages, investigational and control vaccines, and total number of subjects exposed to the MenACWY and control vaccines, is provided in Module 5, section 5.2. The studies that provide full safety information are shown below in Table 1.1.2-1.

Table 1.1.2-1 Overview of Studies That Provide MenACWY Safety Data

Region	Study	Age range	Vaccines	Number of Subjects Exposed	Planned Duration of Study (days) for Each Subject
US	V59P13 phase 3	11-55 y	MenACWY[a]	2649	180
			Menactra	875	
Latin America (Argentina/ Columbia)	V59P17 phase 3	19-65 y [b]	MenACWY[a]	1600 [d] subjects 19-55; 217 [d] subjects 56-65	180
			Menactra	889 [d] subjects 19-55	
			Menomune	109 subjects 56-65	
Latin America (Costa Rica)	V59P18 phase 3	11-18 y	MenACWY[a] + Tdap[c] + HPV	540	211
			MenACWY[a] followed by Tdap [c]	541	271
			Tdap [c] followed by ACWY	539	
US	V59P6 phase 2	11-17 y	MenACWY[a]	151	360
			MenACWY adjuvanted	164	
			Menomune	209	
Europe (Italy)	V59P11 phase 3	11-25 y	MenACWY[a]	357	181
			Tdap [c] + MenACWY[a]	359	
			Tdap [c]	353	

[a] nonadjuvanted final MenACWY formulation
[b] Subjects 56-65 years of age are not in the age range for the proposed indication and are excluded from BLA safety analysis.
[c] Tdap in V59P11 was the licensed European Union (EU) formulation; Tdap in V59P18 was the formulation licensed in the United States (US).
[d] Twenty subjects were exposed but did not provide safety information: twelve of the 1600 MenACWY subjects 19-55 years of age, one of the 217 MenACWY subjects 56-65 years of age, and 7 of the 889 Menactra subjects 19-55 years of age.

1.1.3 Safety Monitoring

The assessment of safety in the three pivotal (please see CSRs V59P13, V59P17, and V59P18) and two supportive (CSRs V59P6 and V59P11) studies was based on relevant guidances and recommendations of the Food and Drug Administration (FDA) in the United States. Table 1.1.3-1 summarizes the safety data recorded during the different time periods postvaccination.

Table 1.1.3-1 Safety Monitoring

Occurrence	Monitoring Interval
Solicited AEs [a]	Day 1 to 7
All unsolicited AEs	Day 1 to 7
Any AE necessitating a physician visit, Emergency Department (ER) visit, or premature withdrawal of subject	Day 8 to 29 [b]
Any medically significant AE necessitating a physician visit, Emergency Department (ER) visit, or premature withdrawal of subject [c]	Day 30 to 180
SAEs	Day 1 to 180 [d]

[a] Solicited local and systemic reactions, subject stayed at home, or analgesic/antipyretic use.
[b] V59P18 monitored day 8 to 31.
[c] Excludes preplanned visits, medical office visits, or emergency room (ER) visits for routine medical care and common acute conditions such as upper respiratory tract infections (URI), otitis media, pharyngitis, urinary tract infections (UTI), gastroenteritis, superficial skin infections, and contact dermatitis. Excluded conditions were not collected from day 30 to day 180.
[d] SAEs were recorded from vaccination until the end of the 6-month follow-up and, if ongoing at 6 months, were monitored until resolution, diagnosis, or further follow-up was no longer clinically indicated.

Safety measures included:

Immediate reactions: signs or symptoms of anaphylaxis, local injection site, and systemic reactions within 30 minutes after each vaccination;

Solicited AEs: (local and systemic reactions and other indicators of reactogenicity [stayed home due to reaction, use of analgesic/antipyretic medication, body temperature]) for 7 days after each vaccination;

All unsolicited AEs, for 7 days after each vaccination, as defined by ICH E2A with input from WHO Collaborative Centre: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;

AEs that require a medical office or Emergency Department (ER) visit, consultation, and/or results in premature withdrawal from the study from day 8 through 28 days after vaccination (day 29);

Medically significant AEs that require a medical office visit, ER visit, or lead to a subject's withdrawal, or hospitalization throughout the study including 6-month follow-up period for subjects who terminate early. Excluded visits were preplanned medical office visits or ER visits for routine medical care and common acute conditions such as:

- Upper respiratory tract infections;
- Otitis media;
- Pharyngitis;
- Urinary tract infections;
- Gastroenteritis;
- Superficial skin infections;
- Contact dermatitis.

Excluded conditions above were not collected or recorded in CRFs.

Serious adverse events: defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the subject was, in the opinion of the investigator at immediate risk of death from the event as it occurred);
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly or birth defect;
- Requires intervention to prevent permanent impairment or damage;
- Is an important and significant medical event that may not be immediately life-threatening or results in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

In all studies, SAEs were recorded from vaccination until the end of the 6-month follow-up (except for [please see CSR V59P18 section 5.3.5.1.16] for which SAEs were recorded through 3 months postvaccination) and, if ongoing at 6 months, were monitored until resolution, diagnosis, or further follow-up was no longer clinically indicated.

After vaccination, standardized diary cards were provided to the subjects to prompt for the solicited AEs during the first 7 days postvaccination and included additional space to note other adverse events or medication use. At the next clinic visit, these cards were returned to the investigator as source documents, and the data were transcribed onto the CRFs according to the protocol-defined recording specifications. Any solicited AE that continued past day 7 was also to be recorded on the unsolicited AE CRF. In addition, subjects were contacted by telephone and scheduled for follow-up visits as required by their respective study protocols. Solicited AEs were categorized as local reactions, systemic reactions, or other indicators of reactogenicity (Table 1.1.3-2).

Table 1.1.3-2 Solicited Adverse Events

Local Reactions	Systemic Reactions	Other Indicators of Reactogenicity
Injection site pain Erythema Induration	Chills Nausea Malaise Myalgia Arthralgia Headache Rash [a] Fever (body temperature ≥38°C)	Stayed home due to reaction Analgesic/antipyretic medication used

[a] Rash not solicited in CSR V59P6 or V59P11.

Study V59P18, due to its ongoing nature and multiple vaccination schedules, provides AEs during a slightly different set of time periods in this integrated summary of safety. The interim data provided for V59P18 consist of data through approximately day 61. All solicited AEs for the 7 days after each vaccination are included in the summary tables for the data integrated across studies. However, since the full 6-month follow-up data are not yet available, only the unsolicited AEs for day 1 to 29 for V59P18 are included in the across-study data tabulations. The unsolicited event data for day 30 to 61 are excluded from the integrated month 2 to 6 summary tables but can be found in the interim study report (please see CSR V59P18, CSR section 12).

In addition to the SAEs for the three pivotal and two supportive studies for the 11 to 55 years of age indication, all SAEs reported in subjects who received MenACWY for other age groups or formulations are listed in section 2.1.3 (please refer to CSRs V59P1, V59P2, V59P3, V59P4, V59P5, V59P7, V59P8, V59P9, V59P10, V59P14, V59P16, and V59P18 [follow-up after day 61 data]). For the studies that are presently ongoing (V59P14, V59P16, and V59P18), SAEs reported herein are based on those events reported to the Novartis Pharmacovigilance database by 15 FEB 08.

Classification of solicited reactions based in part on CBER guidelines is described in Table 1.1.3-3. The relationship of all AEs and SAEs to MenACWY is defined in Table 1.1.3-4.

Table 1.1.3-3 Severity Classifications: Solicited Adverse Events

Reaction	Classification
LOCAL REACTIONS	
Injection site pain	Mild = No limitation in normal daily activity.
	Moderate = Some limitation in normal daily activity
	Severe = Unable to perform normal daily activity
Erythema, induration	Less than 25 mm
	25 to less than 50 mm
	50 mm or greater
SYSTEMIC REACTIONS	
Fever	38°C-38.9°C
	39°C-39.9°C (severe)
	≥40°C (severe)
Chills, nausea, malaise, myalgia, arthralgia, headache, rash (rash: urticarial or other)	Mild = No limitation in normal daily activity.
	Moderate = Some limitation in normal daily activity
	Severe = Unable to perform normal daily activity

Table 1.1.3-4 Vaccine Relationship Definitions

Not related	The AE is not related if exposure to the investigational product has not occurred, OR the occurrence of the AE is not reasonably related in time, OR the AE is considered unlikely to be related to use of the investigational product (i.e. there are no facts (evidence) or arguments to suggest a causal relationship.
Possibly related	The administration of the investigational product and AE are considered reasonably related in time AND the AE could be explained by causes other than exposure to the investigational product.
Probably related	Exposure to the investigational product and AE are reasonably related in time AND the investigational product is more likely than other causes to be responsible for the AE, OR is the most likely cause of the AE

Clinical laboratory data were not collected during the five pivotal and supportive studies submitted in the Application. Clinical laboratory tests (chemistry, hematology, and routine urinalyses) were carried out on samples provided by participants in the first two studies conducted under the clinical development plan for MenACWY. Study V59P1 collected samples before vaccination and on days 29 to 36 after study vaccinations (MenACWY with adjuvant), and study V59P3 collected samples before and on days 29 to 35 after study vaccinations (MenACWY with and without adjuvant [i.e., final formulation]) (please see CSR V59P1, CSR section 12.4 and CSR V59P3, CSR section

12.4). No significant abnormal changes in laboratory parameters were seen in either study.

1.1.4 Narratives

Narrative descriptions of study design for three pivotal studies (V59P13, V59P17, and V59P18) and two supportive studies (V59P6 and V59P11) pertinent to the evaluation of safety for the proposed indication are provided in the following section. Brief descriptions of designs of the other studies not included in the proposed indication may be found in Module 5, section 5.2.

1.1.4.1 Studies in the Proposed Indication

Text and in-text summary tables and listings pertinent to the evaluation of safety are located in this section. In-text tables summarize key safety data and reference all additional supportive summaries are located in Appendix 5.3.5.3.2.7.

1.1.4.1.1 Study V59P13

A narrative description of V59P13 study design and efficacy objectives is provided in CSR V59P13, section 5.3.5.3.1.2. A narrative pertinent to the evaluation of safety in V59P13 is provided below.

Study V59P13 was a randomized, phase 3, multicenter, observer-blind, single-vaccination study in the United States in healthy subjects 11 to 55 years of age to compare the safety and immunogenicity of one vaccination of Novartis MenACWY with one vaccination of licensed meningococcal ACWY conjugate vaccine (Menactra). Subjects were immunized and returned to the clinic at 1 month and phoned at 6 months after vaccination to assess safety. Only data from subjects 11 to 55 years of age who received study vaccine and who provided safety data are evaluated for safety.

The number of MenACWY subjects evaluable for safety was 2649. The planned postvaccination period for each subject was 180 days.

Criteria for evaluation: Solicited AEs from vaccination (day 1) through day 7 after vaccination, all unsolicited AEs from day 1 through day 7, medically attended AEs from day 8 through day 29, AEs considered medically significant or leading to withdrawal from the study from day 30 through 6 months postvaccination, and SAEs throughout the study. The primary safety objective was to compare the percentage of subjects presenting at least one severe systemic reaction after MenACWY to the percentage of subjects presenting at least one severe systemic reaction after Menactra during the first 7 days (days 1 to 7). MenACWY was to be considered noninferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference ($P_{MenACWY}$ minus $P_{Menactra}$) was less than 6%, where $P_{MenACWY}$ and $P_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7

days (day 1 to day 7). Secondary safety objectives included: To describe and compare the safety profile following a single injection of MenACWY (3 lots combined) to that following a single injection of Menactra administered to healthy adolescents or adults (11 to 55 years of age) defined as the percentage and number of subjects with: immediate hypersensitivity reactions (within 30 minutes) following vaccination; local and systemic reactions during the day 1 to 7 period; AEs reported during the day 1 to 29 period; medically significant AEs reported during the day 30 to 180 period; and SAEs reported during the day 1 to 180 period.

Safety results: The primary safety result demonstrated that MenACWY was noninferior to Menactra in terms of severe systemic reactions (i.e., the upper limit of the 2-sided 95% CI of the difference in the percentage of subjects experiencing at least one severe reaction (e.g., 2%) was below 6% [1% difference between vaccine groups with 95% CI of -1, 2]). Both study vaccines were well tolerated with similar reactogenicity profiles. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study. A full description of the safety results of study V59P13 is provided in the final clinical study report in section 5.3.5.1.

1.1.4.1.2 Study V59P17

A narrative description of V59P17 study design and efficacy objectives is not provided in CSR V59P17, section 5.3.5.1.15, since immunogenicity data were a secondary objective and were not included in this application. A narrative pertinent to the evaluation of safety in V59P17 is provided below.

Study V59P17 was a phase 3, multicenter, observer-blind, single-vaccination study in Argentina and Columbia in 2505 randomized, healthy subjects 19 to 55 years of age to compare the safety and immunogenicity of one vaccination of MenACWY with one vaccination of licensed meningococcal ACWY conjugate vaccine (Menactra), and in 326 healthy subjects 56 to 65 years of age to compare the safety and immunogenicity of one vaccination of MenACWY with one vaccination of licensed meningococcal ACWY polysaccharide vaccine (Menomune). Subjects were immunized and returned to the clinic at 1 month, and phoned at 6 months, after vaccination to assess safety and immunogenicity of MenACWY, Menactra, and Menomune vaccines. Only data from subjects 19 to 55 years of age receiving either MenACWY or Menactra are evaluated for safety.

The number of MenACWY subjects evaluable for safety was 1588. The planned postvaccination period for each subject was 180 days.

Criteria for evaluation: Solicited AEs from vaccination (day 1) through day 7 after vaccination, all unsolicited AEs from day 1 through day 7, medically attended AEs from day 8 through day 29, AEs considered medically significant or leading to withdrawal from the study from day 30 through 6 months postvaccination, and SAEs throughout the study. The primary objective of the study was to compare the percentage of subjects

presenting at least one severe systemic reaction after MenACWY to the percentage of subjects presenting at least one severe systemic reaction after Menactra during the first 7 days (days 1 to 7). MenACWY was considered noninferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference ($P_{MenACWY}$ minus $P_{Menactra}$) was less than 6%, where $P_{MenACWY}$ and $P_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (day 1 to day 7).

Safety results: The primary safety results demonstrated that MenACWY was noninferior to Menactra in terms of severe systemic reactions (i.e., the upper limit of the 2-sided 95% CI of the difference in the percentage of subjects experiencing at least one severe reaction (e.g., 3%) was below 6% [1% difference between groups with 95% CI of -1, 3]). Both study vaccines were well tolerated with similar reactogenicity profiles. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study. A full description of the safety results of study V59P17 is provided in the final clinical study report in section 5.3.5.1.

1.1.4.1.3 Study V59P18

A full narrative description of V59P18 study design and efficacy objectives is provided in CSR V59P18, section 5.3.5.1.16. A narrative pertinent to the evaluation of safety in V59P18 is provided below.

Study V59P18 was a phase 3, single-center, open-label, multiple-vaccination study in Costa Rica in 1620 healthy adolescents 11 to 18 years of age to evaluate the safety and immunogenicity of Novartis MenACWY administered either alone or concomitantly with combined tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine (GlaxoSmithKline [GSK], US-licensed Boostrix), and quadrivalent human papillomavirus [type 6, 11, 16, 18] (HPV) recombinant vaccine (Merck & Co., GARDASIL). Subjects were randomized into three groups: one that received MenACWY, Tdap, and HPV concomitantly followed by two additional HPV vaccinations at 60 and 180 days after concomitant vaccination; one that received MenACWY followed by Tdap 30 days later followed by three vaccinations of HPV at 60, 120, and 240 days after concomitant vaccination; and one that received Tdap alone followed by MenACWY 30 days later and three vaccinations of HPV at 60, 120, and 240 days after Tdap alone. The concomitant MenACWY and Tdap group was immunized and returned to the clinic at 1, 2, 6, and 7 months to assess safety and immunogenicity. The MenACWY followed by Tdap group was immunized and returned to the clinic at 1, 2, 4, 8, and 9 months to assess safety and immunogenicity. The Tdap followed by MenACWY group was also immunized and returned to the clinic at 1, 2, 4, 8, and 9 months to assess safety and immunogenicity. Only data through 2 months after vaccination are evaluated for safety.

The number of subjects evaluable for safety was 1620. The planned postvaccination period for each subject randomized to receive MenACWY with concomitant Tdap and HPV was 211 days; for all other subjects it was 271 days.

Criteria for evaluation: Solicited AEs from vaccination (day 1) through day 7 after each vaccination, unsolicited AEs from day 1 through 30 days after last immunization, and medically significant AEs and SAEs reported throughout the study. The safety objectives were to (a) describe and compare the safety profile following a single vaccination of MenACWY given alone or at 1 month after Tdap to the safety profile following a single vaccination of MenACWY given alone 1 month before Tdap, and (b) describe the safety profile following a single vaccination of MenACWY given alone or concomitantly with Tdap and HPV.

Safety results: The safety results showed that both the concomitant and sequential vaccine regimens were safe and well tolerated. When MenACWY was administered alone, the percentage of subjects reporting solicited AEs (any, local, systemic, and other reactions observed during the 7 days after any vaccination) was broadly similar to that when administered 1 month after Tdap (69% vs 64%) but lower than that following MenACWY administered concomitantly with Tdap and HPV (89%). This difference was partly driven by the higher reactogenicity of Tdap. The percentages reporting solicited AEs were higher when Tdap was administered alone (82%) than one month after MenACWY (70%), with 89% reporting reactions after concomitant administration of Tdap with MenACWY and HPV. The decrease in overall reactogenicity to ACWY on the second vaccination may reflect reduced reporting rates; this decrease was also observed for the second vaccination with Tdap. Unsolicited AEs were infrequent and did not show any clear pattern with respect to vaccine group. In conclusion, interim safety results of this study suggest that MenACWY and Tdap vaccines can be given either concomitantly (together with HPV) or sequentially with comparable safety profiles.

A detailed description of the interim safety results of study V59P18 is provided in the preliminary clinical study report in section 5.3.5.1.

1.1.4.1.4 Study V59P6

A full narrative description of V59P6 study design and efficacy objectives is provided in CSR V59P6, section 5.3.5.1.8. A narrative pertinent to the evaluation of safety in V59P6 is provided below.

Study V59P6 was a two-stage, randomized, phase 2, single-blind, single-vaccination study in the United States in a total of 511 healthy adolescents 11 to 17 years of age to compare the immunogenicity, safety, and tolerability of either the adjuvanted or nonadjuvanted formulation of MenACWY with the immunogenicity of a single vaccination of Menomune. Adolescent subjects were immunized and returned to the clinic at 1 month and 1 year, and phoned at 6 months, after vaccination to assess safety and tolerability of test and control vaccines. During the conduct of the trial, the

nonadjuvanted MenACWY formulation was chosen for further development. At that time, the V59P6 study design was amended to add a group that received Novartis MenACWY without adjuvant as stage 2 of the study. Only data from V59P6 subjects who received the nonadjuvanted MenACWY formulation or Menomune are evaluated for safety.

The number of nonadjuvanted MenACWY subjects evaluable for safety was 151. The planned postvaccination period for each subject was 360 days.

Complete results for study V59P6, including results from subjects who received the adjuvanted Novartis MenACWY formulation during stage 1, are provided in the clinical study report in section 5.3.5.1.

Criteria for evaluation: Solicited AEs from vaccination (day 1) through day 7 after vaccination, all unsolicited AEs from day 1 through day 7, medically attended AEs from day 8 through day 29, AEs considered medically significant or leading to withdrawal from the study from day 30 through 6 months postvaccination, and SAEs throughout the study.

Safety results: A single vaccination of nonadjuvanted or adjuvanted MenACWY was well tolerated by healthy adolescents 11 to 17 years of age. The incidence of severe local and systemic reactogenic events was low in all groups (less than 7% in the MenACWY groups and less than 4% in the Menomune groups) and of limited duration (all resolved completely or decreased in intensity within 2 days after onset). None of the SAEs were considered by the investigator to be related to study vaccine administration. No unexpected or otherwise clinically significant AEs related to study vaccines were reported. A full description of the safety results of study V59P6 is provided in the final clinical study report in section 5.3.5.1.

1.1.4.1.5 Study V59P11

A narrative description of V59P11 study design and efficacy objectives is provided in CSR V59P11, section 5.3.5.1.13. A narrative pertinent to the evaluation of safety in V59P11 is provided below.

Study V59P11 was a randomized, phase 3, multicenter, observer-blind, single-vaccination study in Italy in a total of 1069 healthy subjects 11 to 25 years of age to compare the immunogenicity and safety of the concomitant IM administration of a combined tetanus, reduced Tdap vaccine (GSK, Boostrix, licensed in the European Union [EU]) and Novartis MenACWY with either one IM vaccination of Tdap with saline or one vaccination of MenACWY with saline.

Subjects received a single administration of study vaccine and returned to the clinic at 1 month and 6 months after vaccination for evaluation of the safety and immunogenicity of test and control vaccines.

The number of subjects evaluable for safety was 1069. The planned postvaccination period for each subject was 181 days.

Criteria for evaluation: Solicited AEs from vaccination (day 1) through day 7 after vaccination, all unsolicited AEs from day 1 through day 7, medically attended AEs from day 8 through day 29, AEs considered medically significant or leading to withdrawal from the study from day 30 through 6 months postvaccination, and SAEs throughout the study.

Safety results: The percentages of subjects in the MenACWY + saline group reporting any solicited AE, local AEs, and systemic AEs within 7 days after vaccination were lower than in the Tdap + MenACWY or Tdap + saline groups. No unexpected or otherwise clinically significant, unsolicited AEs related to the vaccines administered were reported. A full description of the safety results of study V59P11 is provided in the final clinical study report in section 5.3.5.1.

1.1.4.2 Supportive Studies Providing SAE Listings

The studies providing only SAE listings are V59P1, V59P2, V59P3, V59P4, V59P5, V59P7, V59P8, V59P9, V59P10, V59P14, V59P16, V59P18 (after day 61). Descriptions of these studies are provided in individual CSRs in section 5.3.5.4.

1.2 Overall Extent of Exposure

Subjects in the three pivotal and two supportive studies were randomly assigned to receive a single vaccination of the final MenACWY formulation alone on the day (day 1) of vaccination ("**MenACWY Alone**": total of 5286 subjects), a single vaccination of MenACWY with concomitant vaccines Tdap or HPV and Tdap on day 1 ("**MenACWY + ConVax":** 899 subjects), or a single vaccination of MenACWY at day 31 following Tdap at day 1 ("**Tdap Alone**": 539 subjects in V59P18) (Table 1.2-1). A total of 6724 subjects were exposed to MenACWY as a single first vaccination or second vaccination in these studies.

By comparison, the following numbers of subjects were randomly assigned to the licensed control groups: Menactra, 1757 subjects; Menomune, 209 subjects; and Tdap with saline, 353 subjects (Table 1.2-1). Although the 353 subjects in the Tdap-saline comparison group received the EU-marketed Tdap formulation, the data were combined with the US-licensed formulation in some analyses because of the close similarity between the two formulations. The slightly higher aluminium content in the EU formulation (0.5 mg of aluminum as salts vs. 0.39 mg in the US formulation) and the addition of 2.5 mg of 2-phenoxyethanol added as a preservative (versus none in the US formulation) was not considered to materially affect the safety profile.

The composition of vaccines is given in the individual study reports (sections 5.3.5.3 and 5.3.5.4), and the antigens included in each formulation are summarized in Module 2,

section 2.7.2.1. Table 1.2-1 shows the numbers of MenACWY subjects who received one vaccination of the final formulation of MenACWY and had safety data available.

In the complex concomitant and sequential vaccination regimens employed in study V59P18 (please refer to CSR V59P18, section 5.3.5.1.16):

- The 541 subjects who first received MenACWY at day 1 followed by Tdap at day 31 and HPV at day 61, day 121, and day 241 are evaluated for reactogenicity as "**MenACWY Alone**" subjects based on results obtained within 7 days after MenACWY vaccination; these subjects are also evaluated for the incidence of unsolicited AEs, SAEs, and other medically significant AEs as "MenACWY Alone" subjects within 1 month after MenACWY vaccination;
- The 540 subjects who received MenACWY concomitantly with Tdap and HPV at day 1 followed by HPV alone at day 61 and day 181 are evaluated for reactogenicity as "**MenACWY + ConVax** (concomitant vaccines)" subjects within 7 days after MenACWY day 1 vaccination and for unsolicited AEs, etc., within 1 month after vaccination;
- The 539 subjects who received Tdap at day 1 followed by MenACWY at day 31 and HPV at day 61, day 121, and day 241 are evaluated for reactogenicity as "**Tdap Alone**" within 7 days after day 1 vaccination and for unsolicted AEs, etc., within 1 month after Tdap vaccination. Reactogenicity of MenACWY at day 31 after receipt of Tdap on day 1 is also included within this document.

For all studies, subjects classified as **"MenACWY Alone"** and **"MenACWY + ConVax"** subjects were combined and evaluated for reactogenicity as "**Total MenACWY**" subjects.

Subjects from V59P18 are included in the unsolicited reactogenicity summaries for the first month postvaccination. V59P18 subjects are not included in the evaluation of unsolicited adverse events that occurred during the second through sixth months following day 1 vaccination, since this study is still ongoing and complete data for this period are not yet available.

Table 1.2-1 Summary of Subject Populations: Number Exposed to MenACWY, MenACWY with Concomitant Vaccines, and Licensed Comparator Vaccines Who Have Safety Data

Age Group Study	Number of Subjects Exposed Who Have Available Safety Data (Safety Population)					
	MenACWY Alone	MenACWY+ ConVax [d]	Total ACWY [e]	Menactra	Menomune	Tdap
11-18 years						
V59P6 [a]	**151**		**151**		**209**	
V59P11 [b]	**357**	**359**	**716**			**353**
V59P13	**1631**		**1631**	**539**		
V59P18 [c]	**541**	**540**	**1081**			**539**
19-34 years						
V59P13	**307**		**307**	**105**		
V59P17	**838**		**838**	**464**		
35-55 years						
V59P13	**711**		**711**	**231**		
V59P17	**750**		**750**	**418**		
Total	**5286**	**899**	**6185**	**1757**	**209**	**892**

Appendix 5.3.5.3.2.7 Table 1. Cell entries are number of subjects.
[a] Subjects from V59P6 who received adjuvanted MenACWY are excluded.
[b] Subjects in V59P11 are 11-25 years of age.
[c] Subjects in V59P18 who received MenACWY followed by Tdap are included under the MenACWY column here and for the adverse events occurring during the first month after vaccination. Similarly, subjects who received Tdap followed by MenACWY are included under the Tdap column. Subjects from V59P18 are not included in the summaries of unsolicited adverse events occurring during the second through sixth months after vaccination. Data for the full duration of month 2 through month 6 are not yet available because this study is still ongoing.
[d] Subjects in V59P11 received MenACWY + Tdap (EU-marketed formulation); subjects in V59P18 received MenACWY + HPV + Tdap (US-licensed formulation).
[e] All subjects who received either MenACWY alone or with a concomitant vaccine (column 1 + column 2).

More than 99% of the subjects enrolled were exposed to MenACWY and/or licensed concomitant vaccines. All subjects for the proposed indication who were enrolled, received at least one vaccination with study vaccines, and provided safety data were included in safety analyses. Subjects exposed to vaccine but who provided no safety data were excluded.

Ninety-six percent of 11 to 18 year subjects, 98% of 19 to 34 year subjects, and 99% of 35 to 55 year subjects either completed the studies through 6 months (V59P11, V59P13, and V59P17), through 12 months (V59P6), or continued participation through day 61 (V59P18) (Tables 1.2-3 and 1.2-4).

Percentages of subjects who prematurely withdrew were similar between total MenACWY and Menactra (Table 1.2-2) and within individual age groups pooled across studies (Tables 1.2-3 and 1.2-4).

A summary of premature withdrawal and the reasons for withdrawal from each study is provided in section 5.3.5.3.1, Table 3.1.2-1.

Table 1.2-2 Subject Disposition and Reasons for Withdrawal: Comparing Total MenACWY and Menactra Pooled Across Age Groups and Studies

Subject Sample	Subject Disposition		Total ACWY [a]	Menactra
Pooled Age Groups and Studies	Total exposed: n		6185	1757
	Total ongoing: n (%)		996 (16)	0
	Total completed: n (%)		5024 (81)	1731 (99)
	Premature withdrawal: n (%)	AE	1 (<1)	0
		Withdrew consent	60 (1) [b]	3 (<1)
		Lost to follow up	89 (1)	21 (1)
		Other	15 (<1)	2 (<1)

Appendix 5.3.5.3.2.7 Table 4.

[a] All subjects who received MenACWY alone and those who received MenACWY with concomitant vaccines.

[b] 58 of 60 came from study V59P18, where no Menactra was administered.

Table 1.2-3 Subject Disposition and Reasons for Withdrawal: Comparing Vaccines Pooled Across Studies Within the 11 to 18 Year Age Group

Age (yr)	Subject Disposition		ACWY Alone	ACWY + Concomitant Vaccines	Total ACWY	Menactra	Menomune	Tdap
11-18	Total exposed: n		2680	899	3579	539	209	892
	Total ongoing [a]: n (%)		495 (18)	501 (56)	996 (28)	0	0	488 (55)
	Total completed: n (%)		2094 (78)	352 (39)	2446 (68)	524 (97)	203 (97)	349 (39)
	Premature Withdrawal	AE	0	1 (<1)	1 (<1)	0	0	0
		Withdrew consent	36 (1)	24 (3)	60 (2)	2 (<1)	1 (<1)	31 (3)
		Lost to follow up	47 (2)	14 (2)	61 (2)	12 (2)	5 (2)	19 (2)
		Other	8 (<1)	7 (1)	15 (<1)	1 (<1)	0	5 (<1)

Appendix 5.3.5.3.2.7 Table 5.1. First vaccine given is listed in column header.
[a] Study V59P18 is ongoing. CSR expected 4Q08.

Table 1.2-4 Subject Disposition and Reasons for Withdrawal: Comparing Vaccines Pooled Across Studies Within 19 to 34 and 35 to 55 Year Age Groups

Subject Disposition		19 to 34 Age Group		35 to 55 Age Group	
		ACWY	Menactra	ACWY	Menactra
Total exposed: n		1145	569	1461	649
Total ongoing: n (%)		0	0	0	0
Total completed: n (%)		1124 (98)	563 (99)	1454 (100)	644 (99)
Premature Withdrawal	AE	0	0	0	0
	Withdrew consent	0	1 (<1)	0	0
	Lost to follow up	21 (2)	5 (<1)	7 (<1)	4 (<1)
	Other	0	0	0	1 (<1)

Appendix 5.3.5.3.2.7 Tables 5.2 and 5.3.

1.3 Demographic and Other Characteristics of Study Subjects

Demographic and other baseline characteristics for randomized subjects are presented for individual studies in section 5.3.5.3.1.3.1 and in individual CSRs in section 5.3.5.1.

Inclusion and exclusion criteria were similar in all five studies. Only healthy individuals (based on medical history, physical examination findings, and clinical judgment of the investigator) were enrolled into the studies. Subjects were ineligible for the studies if they had any serious chronic or progressive disease (e.g., any history of neoplasm, insulin-dependent diabetes, cardiac disease, autoimmune disease, human immunodeficiency virus infection or acquired immunodeficiency syndrome, or blood dyscrasias with signs of cardiac or renal failure or severe malnutrition); epilepsy or any progressive neurological disease; history of any anaphylactic shock; pulmonary reactivity; urticaria, or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component; known or suspected disease of the immune system, including individuals who were receiving immunosuppressive therapy, including use of any systemic corticosteroids; had taken systemic antibiotics (either oral or parenteral) within the previous 7 to 14 days; known to have a bleeding diathesis or any condition that may have been associated with a prolonged bleeding time; or had Down's syndrome or other known cytogenic disorders. Inclusion and exclusion criteria for the individual studies are found in Appendix 16.1.1 (study protocol) of CSRs in section 5.3.5.1.

Eligibility criteria were met by at least 99% of subjects enrolled in the studies (Appendix 5.3.5.3.2.7 Table 2). Subjects who were found to have not met entrance requirements are described in the individual clinical study reports in section 5.3.5.1.

Demographic and baseline characteristics within individual age groups are discussed in section 1.3.1.

Geographic differences in demographic and baseline characteristics, reactogenicity, and AE occurrence are discussed in section 5.2.

1.3.1 Demographic and Other Characteristics of Study Subjects for Total MenACWY Compared With Menactra and by Age Group

Demographic and other baseline characteristics were similar between MenACWY and control vaccine groups within each of the five studies, as described in individual CSRs in section 5.3.5.1. Accordingly, the following sections summarize prevaccination characteristics (a) pooled across age groups (11 to 18 years, 19 to 34 years, and 35 to 55 years) and studies; and (b) across vaccine groups (MenACWY alone, MenACWY plus concomitant vaccines, total MenACWY, Menactra, Menomune, and Tdap) for pooled studies within each age group.

Section 1.3.1.1 summarizes the demographic and other baseline characteristics of total MenACWY and Menactra subjects pooled across age groups and within each age group.

Section 1.3.1.2 summarizes prevaccination characteristics by vaccine group within each age group pooled across studies.

1.3.1.1 Total MenACWY Compared With Menactra

Demographic and baseline characteristics of total MenACWY compared with Menactra across age groups are listed in Table 1.3.1.2-1.

Demographic and baseline characteristics of total MenACWY and Menactra were similar in all respects (Table 1.3.1.2-1). A difference in mean age was noted, 23.5 years in total MenACWY and 29.2 years in Menactra groups, reflecting the contribution of the adolescent-only studies V59P18, V59P6, and V59P11, in which Menactra was not administered. Approximately 60% of subjects were female, and nearly 90% of subjects were Caucasian or Hispanic.

In conclusion, demographic and other baseline characteristics were judged to be similar between total MenACWY and Menactra subjects pooled across studies and age groups. Any apparent differences were most likely due to effects of varying randomization ratios in individual studies.

1.3.1.2 Total MenACWY Across Age Groups

As expected, certain demographic and baseline characteristics of 11 to 18 year, 19 to 34 year, and 35 to 55 year age groups differed as a function of age (Table 1.3.1.2-1). Ages

averaged 14.1 years, 26.5 years, and 44.0 years, respectively. Mean weight and height also varied among the age groups.

An imbalance in the male:female ratio was noted, as the proportion of males decreased as age group increased (50%, 33%, and 26%, respectively). Additionally, the proportions of Caucasian subjects varied as age groups increased (59%, 32%, and 48%); correspondingly, the proportions of Hispanic subjects also varied as age groups increased (34%, 57%, and 42%). Other demographic and baseline characteristics were similar among 11 to 18 year, 19 to 34 year, and 35 to 55 year age groups.

Table 1.3.1.2-1 Demographic and Baseline Characteristics: Total MenACWY Compared With Menactra in Pooled Age Groups, Pooled Studies, and 11 to 18, 19 to 34, and 35 to 55 Year Age Groups

Parameter or Characteristic	Total MenACWY			Pooled Age Groups	
	11-18 yr group	19-34 yr group	35-55 yr group	Total MenACWY	Menactra
Total subjects exposed: N	3579	1145	1461	6185	1757
Age (yr): mean (SD)	14.1 (2.4)	26.5 (4.5)	44.0 (5.7)	23.5 (12.9)	29.2 (13.4)
Male : female (%)	50 : 50	33 : 67	26 : 74	41 : 59	37 : 63
Race: n (%)					
Asian	49 (1)	13 (1)	25 (2)	87 (1)	26 (1)
Black	140 (4)	98 (9)	119 (8)	357 (6)	186 (11)
Caucasian	2105 (59)	372 (32)	699 (48)	3176 (51)	810 (46)
Hispanic	1214 (34)	654 (57)	609 (42)	2477 (40)	707 (40)
Other	71 (2)	8 (<1)	9 (<1)	88 (1)	28 (2)
Weight (kg): mean (SD)	57.68 (16.56)	68.23 (16.40)	74.78 (17.21)	63.68 (18.22)	67.59 (18.19)
Height (cm): mean (SD)	161.26 (11.28)	165.86 (9.93)	164.39 (9.82)	162.86 (10.88)	163.38 (10.44)
Did not meet entry criteria: n (%)	17 (<1)	5 (<1)	14 (<1)	36 (<1)	13 (<1)

Appendix 5.3.5.3.2.7 Table 2. Note: Total MenACWY = MenACWY with and without any concomitant vaccine.

In conclusion, as expected, mean subject age, weight, and height increased as a function of age group. Imbalances in male:female ratios of subjects and in relative proportions of Caucasian and Hispanic subjects were also noted, but the pooled data for MenACWY were similar to pooled data for the Menactra group. Thus, the clinical meaningfulness of such differences was considered unlikely. Other demographic and baseline characteristics were similar among age groups.

1.3.2 Demographic and Other Characteristics of Study Subjects by Vaccine Group Within Each Age Group

Demographic and baseline characteristics of MenACWY alone and total MenACWY are compared within each age group with MenACWY with concomitant vaccines, Menactra, Menomune, and Tdap in Table 1.3.2-1.

Comparison of Vaccine Groups Within the 11 to 18 Year Age Group

Demographic and baseline characteristics of vaccine groups pooled across studies were similar in most respects (Table 1.3.2-1). Mean age ranged from 13.9 to 14.2 years, and mean weight ranged from 53.89 to 62.45 kilograms.

The male:female ratio was unbalanced in the pooled analysis (range, 45% to 61% male) but was comparable within individual studies (please see individual CSRs in section 5.3.5.1). Comparisons of reactogenicity between male and female subjects in pooled studies and pooled age groups are provided in section 5.1.2. Additionally, the proportions of Caucasian and Hispanic subjects varied among vaccine groups consistent with geographic location and design of the individual studies. Other demographic and baseline characteristics were similar among the vaccine groups.

In conclusion, demographic and other baseline characteristics with the exception of race/ethnicity were generally similar among the vaccine groups pooled across studies within the 11 to 18 year age group. Because the AE profile of MenACWY was generally similar to the comparator groups within each of the adolescent studies, imbalances in the pooled data are not viewed as being clinically meaningful.

Table 1.3.2-1 Demographic and Baseline Characteristics: Comparing Treatments Within 11 to 18 Year Age Group

11 to 18 Year Age Group						
Parameter Characteristic	**ACWY Alone**	**ACWY + Concomitant Vaccines**	**Total ACWY**	**Menactra**	**Menomune**	**Tdap**
Total subjects exposed: N	2680	899	3579	539	209	892
Age (yr): mean (SD)	14.1 (2.3)	14.1 (2.7)	14.1 (2.4)	14.0 (2.2)	14.2 (1.8)	13.9 (2.6)
Male : female (%)	51 : 49	45 : 55	50 : 50	54 : 46	61 : 39	47 : 53
Race: n (%)						
Asian	48 (2)	1 (<1)	49 (1)	17 (3)	1 (<1)	1 (<1)
Black	138 (5)	2 (<1)	140 (4)	45 (8)	3 (1)	1 (<1)
Caucasian	1757 (66)	348 (39)	2105 (59)	422 (78)	193 (92)	345 (39)
Hispanic	671 (25)	543 (60)	1214 (34)	34 (6)	1 (<1)	543 (61)
Other	66 (2)	5 (<1)	71 (2)	21 (4)	11 (5)	2 (<1)
Weight (kg): mean (SD)	58.69 (17.38)	54.69 (13.37)	57.68 (16.56)	60.09 (18.59)	62.45 (18.42)	53.89 (13.52)
Height (cm): mean (SD)	161.81 (11.58)	159.63 (10.16)	161.26 (11.28)	162.45 (11.77)	165.78 (11.30)	159.17 (10.18)
Did not meet entry criteria: n (%)	16 (<1)	1 (<1)	17 (<1)	5 (<1)	0	1 (<1)

Appendix 5.3.5.3.2.7 Table 3.1.

Comparison of Vaccine Groups Within 19 to 34 Year and 35 to 55 Year Age Groups

As expected, demographic and baseline characteristics of MenACWY and Menactra vaccine groups pooled across studies were similar in all respects within the 19 to 34 year and 35 to 55 year age groups (Table 1.3.2-2), since both of the pivotal studies in these age groups (V59P13 and V59P17) utilized an essentially equivalent study design. Mean ages were 26.5 years and 26.2 years in the 19 to 34 year group and 44.0 years and 44.3 years in the 35 year to 55 year age group for MenACWY and Menactra, respectively.

The male:female ratio was comparable between vaccine groups within each age group. The proportions of Caucasian and Hispanic subjects were similar, as Hispanic subjects were enrolled in greater proportions in the 19 to 34 year group (57% to 61% in MenACWY and Menactra vaccine groups, respectively), reflective of the larger number of Hispanic subjects enrolled in V59P17 in this age group.

In conclusion, demographic and other baseline characteristics were similar among the vaccine groups pooled across studies within the 19 to 34 year and 35 to 55 year age groups.

Table 1.3.2-2 Demographic and Baseline Characteristics: Comparing Treatments Within 19 to 34 and 35 to 55 Age Groups

Parameter or Characteristic	19 to 34 Year Age Group		35 to 55 Year Age Group	
	Total MenACWY	Menactra	Total MenACWY	Menactra
Total subjects exposed: N	1145	569	1461	649
Age (yr): mean (SD)	26.5 (4.5)	26.2 (4.5)	44.0 (5.7)	44.3 (5.8)
Male : female (%)	33 : 67	35 : 65	26 : 74	24 : 76
Race: n (%)				
Asian	13 (1)	7 (1)	25 (2)	2 (<1)
Black	98 (9)	69 (12)	119 (8)	72 (11)
Caucasian	372 (32)	144 (25)	699 (48)	244 (38)
Hispanic	654 (57)	347 (61)	609 (42)	326 (50)
Other	8 (<1)	2 (<1)	9 (<1)	5 (<1)
Weight (kg): mean (SD)	68.23 (16.40)	68.38 (16.72)	74.78 (17.21)	73.13 (16.92)
Height (cm): mean (SD)	165.86 (9.93)	165.53 (9.49)	164.39 (9.82)	162.28 (9.77)
Did not meet entry criteria: n (%)	5 (<1)	1 (<1	14 (<1)	7 (1)

Appendix 5.3.5.3.2.7 Tables 3.2 and 3.3.

2 Adverse Events

2.1 Analysis of Adverse Events

The following categories of safety information were collected. Definition and severity rating scales for each type of event are detailed in Table 1.1.3-3 and include:

- immediate hypersensitivity reactions (within 30 minutes);
- solicited local, systemic, and other reactions (days 1 to 7);
- unsolicited AEs (day 1 through month 6);
  - days 1 to 29 (all unsolicited events);
  - day 30 to month 6 (medically significant AEs necessitating a physician visit, Emergency Department visit, or premature withdrawal of subject)
  - SAEs and medically significant events (in all studies, SAEs were recorded from vaccination until the end of the 6-month follow-up (except for V59P18 for which SAEs were recorded through 1 month after the last vaccination) and, if ongoing at 6 months, were monitored until resolution, diagnosis, or further follow-up was no longer clinically indicated).

Table 2.1-1 summarizes the probabilities of observing at least one AE at various specified rates for the sample sizes included in this application. For example, if an adverse event has a true underlying rate of 0.1% (1/1000), the probability of observing at least one subject in the total MenACWY group with the event was greater than 99%.

Table 2.1-1 Probability of Observing at Least One Event for a Specified Event Rate

Event Rate	Number at Risk	Probability of Observing at Least One Event
1/100	3579[a]	1.000
1/100	5286[b]	1.000
1/100	6185[c]	1.000
1/100	6724[d]	1.000
1/500	3579	0.999
1/500	5286	1.000
1/500	6185	1.000
1/500	6724	1.000
1/1000	3579	0.972
1/1000	5286	0.995
1/1000	6185	0.998
1/1000	6724	0.999
1/3000	3579	0.697
1/3000	5286	0.828
1/3000	6185	0.873
1/3000	6724	0.894
1/5000	3579	0.511
1/5000	5286	0.653
1/5000	6185	0.710
1/5000	6724	0.739
1/10000	3579	0.301
1/10000	5286	0.411
1/10000	6185	0.461
1/10000	6724	0.490

[a] = total number of subjects age 11-18 years who received MenACWY
[b] = total number of subjects age 11-55 years who received MenACWY alone
[c] = total number of subjects age 11-55 years who received MenACWY, either alone or concomitantly with other vaccines
[d] = total number of subjects age 11-55 years who received MenACWY as a first or second vaccination in study-specified vaccination regimen

2.1.1 Common Adverse Events

In all studies in the MenACWY development program, solicited AEs as described in section 1.1 were evaluated on the day of vaccination through 7 days after vaccination. Each type of solicited AE is summarized for subjects by vaccine group and age group for each study and pooled across studies. Summaries of percentages of subjects, severity,

and time of reporting are summarized in the following sections. In each of the three pivotal and two supporting studies, all solicited AEs occurring after vaccination on day 1 through 7 days postvaccination were considered probably or possibly related to the vaccine administered. Listings of solicited AEs for all subjects may be found in individual CSRs (section 5.3.5.1).

2.1.1.1 Solicited Adverse Events: Reactogenicity

2.1.1.1.1 Overview of Incidence and Severity of Solicited Adverse Events Comparing Total MenACWY and Menactra in Pooled Age Groups and Studies

In pooled studies and pooled age groups, an overview of the percentages of subjects with at least one local, systemic, or other reaction, and the worst severity of solicited AEs in these reaction categories, is provided in Table 2.1.1.1.1-1 for total MenACWY and Menactra vaccines. Summaries of individual events comprising each category of solicited reaction are provided in sections 2.1.1.1.3 and 2.1.1.1.4.

The percentages of MenACWY and Menactra subjects who experienced at least one solicited AE (any AE in Table 2.1.1.1.1-1) within 7 days after vaccination were similar (64% MenACWY, 65% Menactra), as were percentages of subjects with any severe reaction (MenACWY, 8%; Menactra, 6%).

The incidence of any solicited local reaction (Table 2.1.1.1.1-1) was slightly lower in MenACWY subjects (47%) than in Menactra subjects (52%), but the incidence of any severe reaction was similar (MenACWY, 4%; Menactra, 3%).

Systemic reactions (Table 2.1.1.1.1-1) to the two vaccines were also similar (MenACWY, 44%; Menactra, 41%) as was the incidence of any severe systemic reactions (MenACWY, 4%; Menactra, 3%).

The incidence of any other reactions was also similar between the two vaccines (MenACWY, 19%; Menactra, 20%: Table 2.1.1.1.1-1).

In conclusion, the incidence of any or severe local, any or severe systemic, or any or severe other reactions to MenACWY in pooled studies and pooled age groups was generally similar to results obtained for Menactra. Severe local and systemic reactions were 1% and 2% higher, respectively, in MenACWY than in Menactra subjects, which was considered not clinically meaningful. Few subjects had severe reactions that continued beyond day 7.

Individual study results are summarized and displayed in section 5.3.5.1 and in section 2.1.1.1.2 by age group.

Table 2.1.1.1.1-1 Overview of Reactogenicity: Total MenACWY vs Menactra: Pooled Age Groups and Pooled Studies

Solicited Reaction	Category	Total MenACWY N=6185 n (%)	Menactra N=1757 n (%)
Any reaction	Any	3966 (64)	1146 (65)
	Severe	507 (8)	110 (6)
Local	Any	2934 (47)	906 (52)
	Severe [a b]	225 (4)	54 (3)
Systemic	Any	2740 (44)	725 (41)
	Severe [a b]	355 (6)	70 (4)
Other [c]	Any [c]	1180 (19)	345 (20)

Appendix 5.3.5.3.2.7 Tables 6 and 10.
Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.
[a] Most severe across all injections. Any severe = severe local reactions or severe systemic reactions.
[b] Severe local reactions = severe erythema, pain, or induration >50 mm; severe fever = ≥ 39.0°C.
[c] Any other reactions = stayed home; analgesic/antipyretic medication use.

2.1.1.1.2 Overview of Incidence and Severity of Reactogenicity by Vaccine Group

Tables 2.1.1.1.2-1 and 2.1.1.1.2-2 provide an overview of reactogenicity results for the 11 to 18, 19 to 34, and 35 to 55 year age groups in the three pivotal and two supportive studies. Description and discussion of results are provided in the CSRs for these studies in section 5.3.5.1.

To briefly summarize the by-study results, the incidence and severity of any, local, systemic, and other reactions were generally similar in the MenACWY groups across all studies and age groups, and were not substantively different in comparison to the Menactra (V59P13, V59P17) or Menomune (V59P6) control groups. In addition, the reactogenicity of MenACWY when given alone was substantially lower than Tdap when given alone in the 11 to 18 year (adolescent) age group in both V59P11 and V59P18. Severe reactions following MenACWY tended to occur at slightly higher rates (1% to 2%) than Menactra or Menomune in adults and adolescents. However, these differences in severe reactions associated with an increased frequency of staying home or using antipyretics/analgesics between the two vaccine groups (Tables 2.1.1.1.2-1 and 2.1.1.1.2-2) and only rarely persisted beyond day 7 (Appendix 5.3.5.3.2.7, Table 49).

Table 2.1.1.1.2-3 compares results for MenACWY alone in the 11 to 18 year age group in studies V59P6, V59P11, V59P13, and V59P18 with results for concomitant vaccines Tdap + MenACWY from study V59P11 and with concomitant MenACWY + HPV +

Tdap from study V59P18. Coadministration of MenACWY with concomitant Tdap or HPV and Tdap produced similar incidence (66% and 75%, respectively) for any reaction and incidence (12% for both concomitant vaccine groups) for any severe reaction compared with MenACWY alone.

Table 2.1.1.1.2-4 compares results for MenACWY alone in the 11 to 18 year age group in studies V59P6, V59P11, V59P13, and V59P18 with those from the V59P18 sequential administration of MenACWY at day 31 following Tdap vaccination at day 1. Tdap administration on day 1 did not affect the incidence or severity of reactions to MenACWY given alone on day 31.

In conclusion, the reactogenicity profile of MenACWY was generally similar to comparator vaccines, and did not substantively change with concomitant or sequential administration of other vaccines in the adolescent age group.

Table 2.1.1.1.2-1 Overview of Reactogenicity: MenACWY Alone vs Control by Study: 11 to 18 Year Age Group

11 to 18 Year Age Group									
		V59P6		V59P11		V59P13		V59P18	
Reaction [a]	Category	ACWY Alone N=151	Menomune N=209	ACWY Alone N=316	Tdap N=315	ACWY Alone N=1631	Menactra N=539	ACWY Alone N=541	Tdap N=539
Any reaction	Any	127 (84)	160 (77)	221 (62)	302 (86)	1044 (64)	379 (70)	373 (69)	443 (82)
	Severe	14 (9)	9 (4)	36 (10)	41 (12)	115 (7)	26 (5)	50 (9)	59 (11)
Local	Any	107 (71)	126 (60)	153 (43)	264 (75)	809 (50)	313 (58)	279 (52)	399 (74)
	Severe [b]	7 (5)	3 (1)	14 (4)	23 (7)	62 (4)	14 (3)	17 (3)	38 (7)
Systemic	Any	85 (56)	102 (49)	171 (48)	202 (57)	710 (44)	234 (43)	274 (51)	309 (57)
	Severe [b]	9 (6)	6 (3)	28 (8)	23 (7)	67 (4)	13 (2)	38 (7)	37 (7)
Other [c]	Any [c]	40 (26)	59 (28)	33 (9)	39 (11)	312 (19)	108 (20)	97 (18)	112 (21)

Appendix 5.3.5.3.2.7 Tables 7.1 and 11.1. Individual CSRs (please see CSR **V59P6**, section 5.3.5.1.8, Tables 14.3.1.1.2 and 14.3.1.1.2.1; **V59P11**, section 5.3.5.1.13, Tables 14.3.1.1.2.1 and 14.3.1.1.2.4; **V59P13**, section 5.3.5.1.14, Tables 14.3.1.1.2 and 14.3.1.1.2.1. **V59P18**, Appendix 5.3.5.3.2.7 Tables 7.1 and 11.1 (visit 1 data only).

[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.

[b] Most severe reaction. Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥ 39.0°C.

[c] Any other reactions = stayed home; analgesic/antipyretic medication use.

Note: V59P17 (CSR V59P17, section 5.3.5.1.15) did not enroll or expose subjects in the 11 to 18 age group.

Table 2.1.1.1.2-2 Overview of Reactogenicity: MenACWY Alone vs Control by Study: 19 to 34 and 35 to 55 Year Age Groups: Studies V59P13 and V59P17

Reaction [a]	Category	19 to 34 Year Age Group				35 to 55 Year Age Group			
		V59P13		V59P17		V59P13		V59P17	
		ACWY Alone N=307	Menactra N=105	ACWY Alone N=838	Menactra N=464	ACWY Alone N=711	Menactra N=231	ACWY Alone N=750	Menactra N=418
Any reaction	Any	211 (69)	63 (60)	532 (63)	299 (64)	394 (55)	143 (62)	423 (56)	262 (63)
	Severe	17 (6)	6 (6)	70 (8)	33 (7)	35 (5)	8 (3)	65 (9)	37 (9)
Local	Any	176 (57)	48 (46)	414 (49)	248 (53)	290 (41)	106 (46)	315 (42)	191 (46)
	Severe [b]	11 (4)	0	29 (3)	20 (4)	22 (3)	3 (1)	31 (4)	17 (4)
Systemic	Any	129 (42)	36 (34)	331 (39)	196 (42)	247 (35)	80 (35)	285 (38)	179 (43)
	Severe [b]	8 (3)	6 (6)	48 (6)	17 (4)	19 (3)	5 (2)	47 (6)	29 (7)
Other [c]	Any [c]	65 (21)	20 (19)	160 (19)	72 (16)	178 (25)	55 (24)	120 (16)	90 (22)

Appendix 5.3.5.3.2.7 Tables 7.2, 7.3, 11.2, and 11.3. Individual CSRs in section 5.3.5.1.

[a] Cell entries are number (percent) of subjects with at least one local and/or systemic reaction.

[b] Any severe = severe local reactions or severe systemic reactions. Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥ 39.0°C.

[c] Any other reactions = stayed home; analgesic/antipyretic medication use.

Table 2.1.1.1.2-3 Overview of Reactogenicity: MenACWY Alone vs MenACWY and Concomitant Vaccines by Study: 11 to 18 Year Age Group

11 to 18 Year Age Group							
		V59P6	V59P11		V59P13	V59P18	
Reaction [a]	Category	ACWY Alone N=151	ACWY Alone N=357	Tdap + ACWY N=359	ACWY Alone N=1631	ACWY Alone N=541	ACWY + HPV + Tdap N=540
Any reaction	Any	127 (84)	221 (62)	236 (66)	1044 (64)	373 (69)	405 (75)
	Severe	14 (9)	36 (10)	42 (12)	115 (7)	50 (9)	63 (12)
Local	Any	107 (71)	153 (43)	102 (28)	809 (50)	279 (52)	289 (54)
	Severe [b]	7 (5)	14 (4)	6 (2)	62 (4)	17 (3)	26 (5)
Systemic	Any	85 (56)	171 (48)	198 (55)	710 (44)	274 (51)	310 (57)
	Severe [b]	9 (6)	28 (8)	41 (11)	67 (4)	38 (7)	50 (9)
Other [c]	Any [c]	40 (26)	33 (9)	42 (12)	312 (19)	97 (18)	133 (25)

Appendix 5.3.5.3.2.7 Tables 8 and 12.

[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.

[b] Most severe reaction. Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥ 39.0°C.

[c] Any other reactions = stayed home; analgesic/antipyretic medication use.

Note: V59P17 did not enroll or expose subjects in the 11 to 18 age group.

Table 2.1.1.1.2-4 Overview of Reactogenicity: MenACWY Alone vs MenACWY After Tdap by Study: 11 to 18 Year Age Group

11 to 18 Year Age Group						
		V59P6	V59P11	V59P13	V59P18	
Reaction [a]	Category	ACWY Alone N=151	ACWY Alone N=357	ACWY Alone N=1631	ACWY Alone N=541	Tdap then ACWY N=503
Any reaction	Any	127 (84)	221 (62)	1044 (64)	373 (69)	322 (64)
	Severe	14 (9)	36 (10)	115 (7)	50 (9)	41 (8)
Local	Any	107 (71)	153 (43)	809 (50)	279 (52)	260 (52)
	Severe [b]	7 (5)	14 (4)	62 (4)	17 (3)	19 (4)
Systemic	Any	85 (56)	171 (48)	710 (44)	274 (51)	215 (43)
	Severe [b]	9 (6)	28 (8)	67 (4)	38 (7)	33 (7)
Other [c]	Any [c]	40 (26)	33 (9)	312 (19)	97 (18)	67 (13)

Appendix 5.3.5.3.2.7 Tables 9 and 13.
[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.
[b] Most severe reaction. Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥ 39.0°C.
[c] Any other reactions = stayed home; analgesic/antipyretic medication use.
Note: V59P17 (CSR V5917, section 5.3.5.1.15) did not enroll or expose subjects in the 11 to 18 age group.

2.1.1.1.3 Summary of Incidence and Severity Comparing Total MenACWY and Menactra in Pooled Studies and Pooled Age Groups

Summaries of the incidence and severity of individual local, systemic, and other signs of reactogenicity for total MenACWY and Menactra vaccines in pooled studies and pooled age groups are provided in Table 2.1.1.1.3-1. In pooled studies and pooled age groups, the most common local reaction was injection site pain for both vaccine groups (total MenACWY, 41%; Menactra, 46%). Erythema (15% and 13%, respectively) and induration (13% to 12%) were reported less frequently. Severe local reactions were infrequently reported and ranged in incidence from 1% to 2%. There were no reports of whole arm swelling.

The most common systemic reactions in total MenACWY and Menactra vaccine groups were headache (total MenACWY, 30%; Menactra, 28%), myalgia (18% and 16%, respectively), malaise (16% and 16%), nausea (10% and 8%), and chills (9% and 7%). Severe systemic reactions ranged in incidence from less than 1% to 3%.

Analgesic/antipyretic use was the most frequently reported other reaction (total MenACWY, 17%; Menactra, 19%). Fever above 39°C was observed at an incidence of less than 1% in both vaccine groups.

In conclusion, the incidence and severity of any local, systemic, and other reactions to total MenACWY in pooled studies and pooled age groups were similar to results obtained for the Menactra group. As noted previously, severe reactions tended to be reported slightly more frequently in the MenACWY group in multiple categories, but few of these reactions persisted past day 7 (AEs noted as severe and possibly/probably related: Appendix 5.3.5.3.2.7 Table 49).

Each individual local, systemic, and other reaction is summarized in section 2.1.1.1.4, which compares the incidence and severity of reactogenic events across vaccine groups.

Table 2.1.1.1.3-1 Summary of Individual Signs of Reactogenicity: Total MenACWY Compared With Menactra in Pooled Studies: Days 1 to 7; Pooled Age Groups

Reaction	Category	Total MenACWY N=6185 n (%)	Menactra N=1757 n (%)
LOCAL REACTIONS			
Pain	Any	2524 (41)	816 (46)
	Severe	100 (2)	36 (2)
Erythema	Any	926 (15)	231 (13)
	>50 mm	97 (2)	17 (1)
Induration	Any	775 (13)	203 (12)
	>50 mm	86 (1)	15 (1)
SYSTEMIC REACTIONS			
Chills	Any	545 (9)	120 (7)
	Severe	53 (1)	6 (<1)
Nausea	Any	625 (10)	142 (8)
	Severe	47 (1)	9 (1)
Malaise	Any	961 (16)	285 (16)
	Severe	107 (2)	22 (1)
Myalgia	Any	1130 (18)	280 (16)
	Severe	104 (2)	17 (1)
Arthralgia	Any	580 (9)	130 (7)
	Severe	61 (1)	10 (1)
Headache	Any	1881 (30)	491 (28)
	Severe	203 (3)	38 (2)
Rash	Any	160 (3)	42 (2)
Fever	38°C - 38.9°C	125 (2)	27 (2)
	39°C - 39.9°C	30 (<1)	8 (<1)
	≥ 40°C	6 (<1)	2 (<1)
OTHER REACTIONS			
Stayed home	Yes	268 (4)	63 (4)
Analgesic/ antipyretic use	Yes	1066 (17)	326 (19)

Appendix 5.3.5.3.2.7, Table 14.

2.1.1.1.4 Summary of Incidence and Severity of Local and Systemic Reactions by Vaccine Group Within the 11 to 18 Year Age Group

Tables 2.1.1.1.4-1 and 2.1.1.1.4-2 summarize reactogenicity results for the 11 to 18, 19 to 34, and 35 to 55 year age groups in the five studies. CSRs for these studies are provided in section 5.3.5.1.

Table 2.1.1.1.4-3 compares results for MenACWY alone in the 11 to 18 year age group in studies V59P6, V59P11, V59P13, and V59P18 with results for concomitant vaccines Tdap + MenACWY from study V59P11 and with concomitant MenACWY + HPV + Tdap from study V59P18.

Table 2.1.1.1.4-4 compares results for MenACWY alone in the 11 to 18 year age group in studies V59P6, V59P11, V59P13, and V59P18 with those from the V59P18 sequential administration of MenACWY at day 31 following Tdap vaccination at day 1.

Individual study results are summarized and displayed in section 5.3.5.1 and in Appendix 5.3.5.3.2.7 Tables 15.1, 15.2, and 15.3 by age group.

Evaluation of solicited AEs is presented separately for each local MenACWY reaction and each systemic reaction in following sections. For subjects who received MenACWY with concomitant medications, only the local reactions at the MenACWY injection site were summarized in the analyses presented here. The measurements taken at the Tdap or HPV sites are summarized in the study CSRs. In general, the findings are relatively consistent across the various age groups and studies and support the overall conclusions listed previously for pooled analyses.

Table 2.1.1.1.4-1 Summary of Individual Signs of Reactogenicity: MenACWY Alone vs Control by Study: Days 1 to 7: 11 to 18 Year Age Group

11 to 18 Year Age Group									
		V59P6		V59P11		V59P13		V59P18	
Reaction [a]	Category	ACWY Alone N=151	Menomune N=209	ACWY Alone N=357	Tdap N=353	ACWY Alone N=1631	Menactra N=539	ACWY Alone N=541	Tdap N=539
LOCAL REACTIONS									
Pain	Any	81 (54)	114 (55)	116 (32)	246 (70)	714 (44)	287 (53)	245 (45)	383 (71)
	Severe	0	2 (1)	10 (3)	17 (5)	16 (1)	7 (1)	8 (1)	29 (5)
Erythema	Any	57 (38)	39 (19)	66 (18)	103 (29)	247 (15)	85 (16)	66 (12)	70 (13)
	>50 mm	5 (3)	0	1 (<1)	3 (1)	36 (2)	7 (1)	3 (1)	1 (<1)
Induration	Any	34 (23)	23 (11)	59 (17)	118 (33)	196 (12)	59 (11)	70 (13)	109 (20)
	>50 mm	6 (4)	1 (<1)	4 (1)	6 (2)	31 (2)	4 (1)	6 (1)	9 (2)
SYSTEMIC REACTIONS									
Chills	Any	24 (16)	16 (8)	47 (13)	41 (12)	127 (8)	38 (7)	66 (12)	70 (13)
	Severe	2 (1)	1 (<1)	6 (2)	3 (1)	9 (1)	1 (<1)	6 (1)	2 (<1)
Nausea	Any	22 (15)	20 (10)	28 (8)	35 (10)	187 (12)	47 (9)	72 (13)	82 (15)
	Severe	2 (1)	2 (1)	4 (1)	2 (1)	10 (1)	4 (1)	4 (1)	2 (<1)
Malaise	Any	23 (15)	21 (10)	43 (12)	57 (16)	177 (11)	65 (12)	110 (20)	115 (21)
	Severe	3 (2)	1 (<1)	5 (1)	5 (1)	16 (1)	5 (1)	7 (1)	6 (1)

11 to 18 Year Age Group									
		V59P6		V59P11		V59P13		V59P18	
Reaction [a]	**Category**	**ACWY Alone N=151**	**Menomune N=209**	**ACWY Alone N=357**	**Tdap N=353**	**ACWY Alone N=1631**	**Menactra N=539**	**ACWY Alone N=541**	**Tdap N=539**
Myalgia	Any	35 (23)	30 (14)	79 (22)	127 (36)	310 (19)	99 (18)	104 (19)	141 (26)
	Severe	1 (1)	0	9 (3)	9 (3)	24 (1)	2 (<1)	7 (1)	11 (2)
Arthralgia	Any	12 (8)	7 (3)	40 (11)	60 (17)	137 (8)	34 (6)	62 (11)	76 (14)
	Severe	0	0	9 (3)	4 (1)	7 (<1)	0	3 (1)	6 (1)
Headache	Any	62 (41)	82 (39)	128 (36)	110 (31)	478 (29)	153 (28)	194 (36)	200 (37)
	Severe	7 (5)	5 (2)	19 (5)	11 (3)	33 (2)	7 (1)	23 (4)	24 (4)
Rash	Any	nd	nd	nd	nd	44 (3)	18 (3)	17 (3)	20 (4)
Fever	38°C - 38.9°C	1 (1)	4 (2)	11 (3)	7 (2)	17 (1)	4 (1)	15 (3)	12 (2)
	39°C - 39.9°C	0	0	3 (1)	0	6 (<1)	0	4 (1)	5 (1)
	≥ 40°C	0	0	0	0	0	0	0	0
OTHER REACTIONS									
Stayed home	Yes	6 (4)	4 (2)	12 (3)	15 (4)	52 (3)	14 (3)	40 (8)	39 (8)
Analgesic/ antipyretic	Yes	39 (26)	59 (28)	31 (9)	38 (11)	293 (18)	104 (19)	73 (13)	92 (17)

Appendix 5.3.5.3.2.7 Table 15.1.

[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.
nd = not done.

Table 2.1.1.1.4-2 Summary of Individual Signs of Reactogenicity: MenACWY Alone vs Control by Study: Days 1 to 7: 19 to 34 and 35 to 55 Year Age Groups: Studies V59P13 and V59P17

Reaction [a]	Category	19 to 34 Year Age Group				35 to 55 Year Age Group			
		V59P13		V59P17		V59P13		V59P17	
		ACWY Alone N=307	Menactra N=105	ACWY Alone N=838	Menactra N=464	ACWY Alone N=711	Menactra N=231	ACWY Alone N=750	Menactra N=418
INJECTION SITE									
Pain	Any	151 (49)	45 (43)	359 (43)	231 (50)	240 (34)	92 (40)	273 (36)	161 (39)
	Severe	1 (<1)	0	18 (2)	14 (3)	2 (<1)	0	23 (3)	15 (4)
Erythema	Any	66 (21)	7 (7)	126 (15)	57 (12)	101 (14)	34 (15)	81 (11)	48 (11)
	>50 mm	10 (3)	0	10 (1)	6 (1)	18 (3)	3 (1)	7 (1)	1 (<1)
Induration	Any	46 (15)	6 (6)	104 (12)	61 (13)	82 (12)	23 (10)	75 (10)	54 (13)
	>50 mm	6 (2)	0	8 (1)	7 (2)	8 (1)	1 (<1)	5 (1)	3 (1)
SYSTEMIC									
Chills	Any	14 (5)	7 (7)	65 (8)	39 (8)	27 (4)	5 (2)	59 (8)	31 (7)
	Severe	1 (<1)	0	10 (1)	3 (1)	0	0	9 (1)	2 (<1)
Nausea	Any	28 (9)	9 (9)	69 (8)	43 (9)	45 (6)	9 (4)	43 (6)	34 (8)
	Severe	3 (1)	0	5 (1)	2 (<1)	1 (<1)	1 (<1)	5 (1)	2 (<1)
Malaise	Any	40 (13)	15 (14)	165 (20)	104 (22)	62 (9)	19 (8)	144 (19)	82 (20)
	Severe	4 (1)	3 (3)	26 (3)	4 (1)	5 (1)	2 (1)	17 (2)	8 (2)

Reaction [a]	Category	19 to 34 Year Age Group				35 to 55 Year Age Group			
		V59P13		V59P17		V59P13		V59P17	
		ACWY Alone N=307	Menactra N=105	ACWY Alone N=838	Menactra N=464	ACWY Alone N=711	Menactra N=231	ACWY Alone N=750	Menactra N=418
Myalgia	Any	55 (18)	21 (20)	105 (13)	63 (14)	87 (12)	29 (13)	92 (12)	68 (16)
	Severe	1 (<1)	2 (2)	15 (2)	3 (1)	4 (1)	3 (1)	10 (1)	7 (2)
Arthralgia	Any	18 (6)	6 (6)	56 (7)	36 (8)	42 (6)	14 (6)	62 (8)	40 (10)
	Severe	0	1 (1)	6 (1)	1 (<1)	4 (1)	2 (1)	10 (1)	6 (1)
Headache	Any	87 (28)	23 (22)	229 (27)	135 (29)	166 (23)	61 (26)	192 (26)	119 (28)
	Severe	4 (1)	3 (3)	23 (3)	12 (3)	12 (2)	2 (1)	26 (3)	14 (3)
Rash	Any	9 (3)	0	30 (4)	13 (3)	16 (2)	2 (1)	23 (3)	9 (2)
Fever	38°C - 38.9°C	2 (1)	1 (1)	19 (2)	13 (3)	4 (1)	0	23 (3)	9 (2)
	39°C - 39.9°C	2 (1)	1 (1)	6 (1)	3 (1)	1 <1)	0	4 (1)	4 (1)
	≥ 40°C	0	0	2 (<1)	0	0	0	2 (<1)	2 (<1)
OTHER REACTIONS									
Stayed home	Yes	7 (2)	3 (3)	40 (5)	22 (5)	10 (1)	0	35 (5)	24 (6)
Analgesic/ antipyretic	Yes	64 (21)	19 (18)	144 (17)	66 (14)	176 (25)	55 (24)	106 (14)	82 (20)

Appendix 5.3.5.3.2.7 Tables 15.2 and 15.3.

[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.

Table 2.1.1.1.4-3 Summary of Individual Signs of Reactogenicity: MenACWY Alone vs MenACWY + Concomitant Vaccines by Study: Days 1 to 7: 11 to 18 Year Age Group

11 to 18 Year Age Group							
		V59P6	V59P11		V59P13	V59P18	
Reaction [a]	Category	ACWY Alone N=151	ACWY Alone N=357	ACWY + Tdap N=359	ACWY Alone N=1631	ACWY Alone N=541	ACWY + HPV + Tdap N=540
LOCAL REACTIONS							
Pain	Any	81 (54)	116 (32)	82 (23)	714 (44)	245 (45)	263 (49)
	Severe	0	10 (3)	6 (2)	16 (1)	8 (1)	16 (3)
Erythema	Any	57 (38)	66 (18)	48 (13)	247 (15)	66 (12)	68 (13)
	>50 mm	5 (3)	1 (<1)	1 (<1)	36 (2)	3 (1)	6 (1)
Induration	Any	34 (23)	59 (17)	41 (11)	196 (12)	70 (13)	68 (13)
	>50 mm	6 (4)	4 (1)	1 (<1)	31 (2)	6 (1)	11 (2)
SYSTEMIC REACTIONS							
Chills	Any	24 (16)	47 (13)	39 (11)	127 (8)	66 (12)	77 (14)
	Severe	2 (1)	6 (2)	3 (1)	9 (1)	6 (1)	7 (1)
Nausea	Any	22 (15)	28 (8)	43 (12)	187 (12)	72 (13)	88 (16)
	Severe	2 (1)	4 (1)	5 (1)	10 (1)	4 (1)	8 (1)
Malaise	Any	23 (15)	43 (12)	65 (18)	177 (11)	110 (20)	132 (24)
	Severe	3 (2)	5 (1)	9 (3)	16 (1)	7 (1)	15 (3)

11 to 18 Year Age Group							
		V59P6	V59P11		V59P13	V59P18	
Reaction [a]	Category	ACWY Alone N=151	ACWY Alone N=357	ACWY + Tdap N=359	ACWY Alone N=1631	ACWY Alone N=541	ACWY + HPV + Tdap N=540
Myalgia	Any	35 (23)	79 (22)	118 (33)	310 (19)	104 (19)	145 (27)
	Severe	1 (1)	9 (3)	16 (4)	24 (1)	7 (1)	17 (3)
Arthralgia	Any	12 (8)	40 (11)	57 (16)	137 (8)	62 (11)	94 (17)
	Severe	0	9 (3)	10 (3)	7 (<1)	3 (1)	12 (2)
Headache	Any	62 (41)	128 (36)	129 (36)	478 (29)	194 (36)	216 (40)
	Severe	7 (5)	19 (5)	25 (7)	33 (2)	23 (4)	31 (6)
Rash	Any	nd	nd	nd	44 (3)	17 (3)	21 (4)
Fever	38°C - 38.9°C	1 (1)	11 (3)	9 (3)	17 (1)	15 (3)	24 (4)
	39°C - 39.9°C	0	3 (1)	2 (1)	6 (<1)	4 (1)	2 (<1)
	≥ 40°C	0	0	0	0	0	2 (<1)
OTHER REACTIONS							
Stayed home	Yes	6 (4)	12 (3)	12 (3)	52 (3)	40 (8)	54 (11)
Analgesic/ antipyretic	Yes	39 (26)	31 (9)	38 (11)	293 (18)	73 (13)	102 (19)

Appendix 5.3.5.3.2.7 Table 16.
[a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.
nd = not done

Table 2.1.1.1.4-4 Summary of Individual Signs of Reactogenicity: MenACWY Alone vs MenACWY After Tdap by Study: 11 to 18 Year Age Group

11 to 18 Year Age Group						
		V59P6	V59P11	V59P13	V59P18	
Reaction [a]	Category	ACWY Alone N=151	ACWY Alone N=357	ACWY Alone N=1631	ACWY Alone N=541	Tdap then ACWY N=503
LOCAL REACTIONS						
Pain	Any	81 (54)	116 (32)	714 (44)	245 (45)	239 (48)
	Severe	0	10 (3)	16 (1)	8 (1)	16 (3)
Erythema	Any	57 (38)	66 (18)	247 (15)	66 (12)	64 (13)
	>50 mm	5 (3)	1 (<1)	36 (2)	3 (1)	6 (1)
Induration	Any	34 (23)	59 (17)	196 (12)	70 (13)	64 (13)
	>50 mm	6 (4)	4 (1)	31 (2)	6 (1)	5 (1)
SYSTEMIC REACTIONS						
Chills	Any	24 (16)	47 (13)	127 (8)	66 (12)	45 (9)
	Severe	2 (1)	6 (2)	9 (1)	6 (1)	6 (1)
Nausea	Any	22 (15)	28 (8)	187 (12)	72 (13)	64 (13)
	Severe	2 (1)	4 (1)	10 (1)	4 (1)	5 (1)
Malaise	Any	23 (15)	43 (12)	177 (11)	110 (20)	87 (17)
	Severe	3 (2)	5 (1)	16 (1)	7 (1)	14 (3)

11 to 18 Year Age Group						
Reaction [a]	**Category**	**V59P6**	**V59P11**	**V59P13**	**V59P18**	
		ACWY Alone N=151	**ACWY Alone N=357**	**ACWY Alone N=1631**	**ACWY Alone N=541**	**Tdap then ACWY N=503**
Myalgia	Any	35 (23)	79 (22)	310 (19)	104 (19)	82 (16)
	Severe	1 (1)	9 (3)	24 (1)	7 (1)	8 (2)
Arthralgia	Any	12 (8)	40 (11)	137 (8)	62 (11)	52 (10)
	Severe	0	9 (3)	7 (<1)	3 (1)	1 (<1)
Headache	Any	62 (41)	128 (36)	478 (29)	194 (36)	138 (27)
	Severe	7 (5)	19 (5)	33 (2)	23 (4)	18 (4)
Rash	Any	nd	nd	44 (3)	17 (3)	13 (3)
Fever	38°C - 38.9°C	1 (1)	11 (3)	17 (1)	15 (3)	24 (5)
	39°C - 39.9°C	0	3 (1)	6 (<1)	4 (1)	6 (1)
	≥ 40°C	0	0	0	0	0
OTHER REACTIONS						
Stayed home	Yes	6 (4)	12 (3)	52 (3)	40 (8)	25 (5)
Analgesic/ antipyretic	Yes	39 (26)	31 (9)	293 (18)	73 (13)	51 (10)

Appendix 5.3.5.3.2.7 Table 17. Individual CSRs (please see CSR **V59P6**, section 5.3.5.1.8, Table 14.3.1.1.3.2; **V59P11**, section 5.3.5.1.13, Table 14.3.1.1.3.1 (vaccination A for local); **V59P13**, section 5.3.5.1.14, Table 14.3.1.1.3.1 (ACWY: sum of lots); **V59P18**, Appendix 5.3.5.3.2.7, Table 17. [a] Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction. nd = not done.

Local Reactions

Injection Site Pain

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the most common local reaction during the 7 days after vaccination was injection site pain after both vaccines (total MenACWY, 41%; Menactra, 46%; Table 2.1.1.1.3-1). Severe pain was reported infrequently (incidence was 2% for both vaccines). The onset of pain was most frequently reported within the first 3 days after vaccination (total MenACWY, 40%; Menactra, 46%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, 11% of recipients of both vaccines reported pain (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of injection site pain following MenACWY alone ranged from 32% in study V59P11 to 54% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Severe injection site pain was infrequently reported and similar across all vaccine groups (range, 0% to 3%). The incidence of injection site pain was higher in the 19 to 34 year recipients of MenACWY and Menactra groups (43% and 49%) than in the 35 to 55 year groups (34% and 36%) (Table 2.1.1.1.4-2). Severe pain in the 19 to 34 and 35 to 55 year groups was infrequently reported and was similar to that noted among the vaccine groups.

In study V59P11, the incidence of pain after MenACWY alone was 32% and after concomitant vaccination with MenACWY and Tdap was 23% (Table 2.1.1.1.4-3). In study V59P18, the incidence of pain was 45% after MenACWY alone and 49% after concomitant MenACWY, Tdap, and HPV. Additionally, the incidence of pain was 45% after MenACWY alone and 49% after sequential administration of Tdap followed by MenACWY (Table 2.1.1.1.4-4). Injection site pain after MenACWY given concomitantly with other vaccines was no worse in incidence and severity than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY reduced the incidence of injection site pain compared to MenACWY alone (MenACWY alone, 32%; MenACWY + Tdap, 23%). Concomitant administration of MenACWY, HPV, and Tdap also did not substantially change the incidence of injection site pain compared to MenACWY alone (MenACWY, 45%; MenACWY + HPV + Tdap, 49%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 45%; Tdap followed 1 month later by MenACWY, 48%) did not substantially change the incidence of injection site pain.

Erythema

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of erythema was 15% and 13%, respectively (Table 2.1.1.1.3-1). Severe erythema was reported infrequently (incidence was 2% and 1%). The onset of erythema was most frequently reported within the first 3 days after vaccination (total MenACWY,

14%; Menactra, 13%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, erythema was reported by 5% and 4%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of erythema following MenACWY vaccination alone ranged from 12% in study V59P18 to 38% in study V59P6 within 7 days after vaccination (Table 2.1.1.1.4-1). Severe erythema was infrequently reported and similar across all vaccine groups (range, less than 1% to 3%). The incidence of erythema in the 19 to 34 year groups (21% and 15%) and in the 35 to 55 year groups (14% and 11%) was similar to that seen in the control groups. Erythema greater than 50 mm in the 19 to 34 and 35 to 55 year groups (Table 2.1.1.1.4-2) was infrequently reported and was similar among the vaccine groups.

The incidence of erythema was 18% after MenACWY alone and 13% after MenACWY and Tdap were given concomitantly in study V59P11 (Table 2.1.1.1.4-3), was 12% after MenACWY alone and 13% after concomitant administration with Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 12% after MenACWY alone and 13% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Erythema after MenACWY and concomitant or sequential vaccinations were given was no worse in incidence and severity than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY also reduced the incidence of erythema compared to MenACWY alone (MenACWY alone, 18%; MenACWY + Tdap, 13%). Concomitant administration of MenACWY, HPV, and Tdap did not substantially change the incidence of erythema compared to MenACWY alone (MenACWY, 12%; MenACWY + HPV + Tdap, 13%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 12%; Tdap followed 1 month later by MenACWY, 13%) also did not substantially change the incidence of erythema.

Induration

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of induration was 13% and 12%, respectively (Table 2.1.1.1.3-1). Induration greater than 50 mm was reported infrequently (incidence was 1% in both vaccine groups). The onset of induration was most frequently reported within the first 3 days after vaccination (total MenACWY, 12%; Menactra, 11%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, induration was reported by 5% and 4%, respectively (Appendix 5.3.5.3.2.7 Table 22). There was one subject in study V59P13 (subject 56/1085) who had an extensive injection site reaction (8 X 13 cm); there was no indication of whole arm swelling.

In the 11 to 18 year age group in individual studies, the incidence of induration following MenACWY alone ranged from 12% in study V59P13 to 23% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Induration greater than 50 mm was infrequently reported and similar across MenACWY groups and MenACWY groups with concomitant administration of Tdap and HPV (range, < 1% to 4%); induration tended to

be slightly less common in the Menactra or Menomune groups, and more common in the Tdap group. The incidence of induration in the 19 to 34 year groups (15% and 12%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (12% and 10%) was similar to that seen in the control groups. Induration greater than 50 mm in the 19 to 34 and 35 to 55 year groups was infrequently reported, and was slightly more common in the MenACWY group.

The incidence of induration was 17% after MenACWY and 11% after MenACWY and Tdap were given concomitantly in study V59P11 (Table 2.1.1.1.4-3), was 13% after both MenACWY alone and after MenACWY was administered concomitantly with Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 13% after both MenACWY alone and after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Incidence and severity of induration after MenACWY was given concomitantly or sequentially with routine vaccines was generally no worse when MenACWY was given alone.

In conclusion, concomitant administration of Tdap with MenACWY also reduced the incidence of induration compared to MenACWY alone (MenACWY alone, 17%; MenACWY + Tdap, 11%). In addition, concomitant administration of MenACWY, HPV, and Tdap did not substantially change the incidence of induration compared to MenACWY alone (MenACWY, 13%; MenACWY + HPV + Tdap, 13%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 13%; Tdap followed 1 month later by MenACWY, 13%) did not substantially change the incidence of induration.

Systemic Reactions

Headache

In pooled studies and pooled age groups, the most common systemic reaction during the 7 days after vaccination was headache in both MenACWY and Menactra recipients (MenACWY, 30%; Menactra, 28%; Table 2.1.1.1.3-1). Severe headache was reported infrequently (3% and 2%, respectively). The onset of headache was most frequently reported within the first 3 days after vaccination (MenACWY, 25%; Menactra, 22%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, headache was reported by 15% and 14%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of headache following MenACWY alone ranged from 29% in study V59P13 to 41% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Severe headache was infrequently reported and similar across MenACWY and control groups (range, 2% to 5%), and occasionally was slightly more common in the MenACWY group. The incidence of headache in the 19 to 34 year groups (28% and 27%) and in the 35 to 55 year groups (23% and 26%; Table 2.1.1.1.4-2) was similar to that seen in the control groups (22% to

29%). Severe headache in the 19 to 34 year (1%) and 35 to 55 year (3%) groups was infrequently reported and was similar among MenACWY and control groups.

The incidence of headache was 36% after both MenACWY alone and MenACWY given concomitantly with Tdap in study V59P11; Table 2.1.1.1.4-3), was 36% after MenACWY alone and 40% after MenACWY was given concomitantly with Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 36% after MenACWY alone and 27% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Thus, headache after MenACWY and concomitant or sequential vaccines were given was generally no worse in incidence and severity than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY did not change the incidence of headache compared to MenACWY alone (MenACWY alone, 36%; MenACWY + Tdap, 36%). Concomitant administration of MenACWY, HPV, and Tdap also did not substantially change the incidence of headache compared to MenACWY alone (MenACWY, 36%; MenACWY + HPV + Tdap, 40%). Sequential administration of Tdap followed by MenACWY alone reduced the incidence of headache compared to MenACWY alone (MenACWY, 36%; Tdap followed 1 month later by MenACWY, 27%).

Myalgia

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of myalgia during the 7 days after vaccination was 18% in the total MenACWY group and 16% in the Menactra group; Table 2.1.1.1.3-1). Severe myalgia was reported infrequently (incidence was 2% and 1%, respectively). The onset of myalgia was most frequently reported within the first 3 days after vaccination (total MenACWY, 16%; Menactra, 13%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, myalgia was reported by 7% and 7%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of myalgia following MenACWY alone ranged from 19% in studies V59P13 and V59P18 to 23% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Severe myalgia was infrequently reported and similar across all vaccine groups (range, 1% to 3%). The incidence of myalgia in the 19 to 34 year groups (18% and 13%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (12% and 12%) was similar to that seen in the control groups. Severe myalgia in the 19 to 34 and 35 to 55 year groups was infrequently reported and was similar among the vaccine groups.

The incidence of myalgia was 22% after MenACWY alone and 33% after MenACWY alone given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 19% after MenACWY alone and 27% after MenACWY was given with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 19% after MenACWY alone and 16% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4).

Thus, as expected, myalgia after MenACWY and concomitant vaccination occurred more frequently than when single vaccines were given, but there was no increase in effect for sequential administration.

In conclusion, concomitant administration of Tdap with MenACWY increased the incidence of myalgia compared to MenACWY alone (MenACWY alone, 22%; MenACWY+ Tdap, 33%). Concomitant administration of MenACWY, HPV, and Tdap also increased the incidence of myalgia compared to MenACWY alone (MenACWY, 19%; MenACWY + HPV + Tdap, 27%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 19%; Tdap followed 1 month later by MenACWY, 16%) slightly reduced the incidence of myalgia.

Nausea

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of nausea during the 7 days after vaccination was 10% in the total MenACWY group and 8% in the Menactra group (Table 2.1.1.1.3-1). Severe nausea was reported infrequently (incidence was 1% in each group). The onset of nausea was most frequently reported within the first 3 days after vaccination (total MenACWY, 8%; Menactra, 6%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, nausea was reported by 4% and 3%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of nausea following MenACWY alone ranged from 8% in study V59P11 to 15% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Severe nausea was infrequently reported and similar across all vaccine groups (1% for all vaccine groups). The incidence of nausea in the 19 to 34 year groups (9% and 8%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (6% and 6%) was similar to that seen in the control groups. Severe nausea in the 19 to 34 and 35 to 55 year groups was infrequently reported and was similar among the vaccine groups.

The incidence of nausea was 8% after MenACWY alone and 12% after MenACWY alone given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 13% after MenACWY alone and 16% after MenACWY was given with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 13% after both MenACWY alone and MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Nausea after MenACWY and concomitant or sequential vaccines were given was no worse in incidence and severity than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY slightly increased the incidence of nausea compared to MenACWY alone (MenACWY alone, 8%; MenACWY + Tdap, 12%). Concomitant administration of MenACWY, HPV, and Tdap also slightly increased the incidence of nausea compared to MenACWY alone (MenACWY, 13%; MenACWY + HPV + Tdap, 16%). Sequential administration of

Tdap followed by MenACWY alone (MenACWY, 13%; Tdap followed 1 month later by MenACWY, 13%) did not substantially change the incidence of nausea.

Chills

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of chills during the 7 days after vaccination was 9% in the total MenACWY group and 7% in the Menactra group; Table 2.1.1.1.3-1). Severe chills was reported infrequently (incidence was no greater than 1% in each group). The onset of chills was most frequently reported within the first 3 days after vaccination (total MenACWY, 7%; Menactra, 5%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, chills was reported by 3% in both groups (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of chills following MenACWY alone ranged from 8% in study V59P13 to 16% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Severe chills was infrequently reported and similar across all vaccine groups (range, 1% to 2%). The incidence of chills in the 19 to 34 year groups (5% and 8%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (4% and 8%) was similar to that seen in the control groups, and was very similar to Menactra. Severe chills in the 19 to 34 and 35 to 55 year groups was infrequently reported and was similar among the vaccine groups.

The incidence of chills was 13% after MenACWY alone and 11% after MenACWY alone given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 12% after MenACWY alone and 14% after MenACWY was given with concomitant Tdap and HPV in study V59P18; Table 2.1.1.1.4-3), and was 12% after MenACWY alone and 9% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Thus, chills after MenACWY and concomitant or sequential vaccines were given was no worse in incidence and severity than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY slightly reduced the incidence of chills compared to MenACWY alone (MenACWY alone, 13%; MenACWY + Tdap, 11%). Concomitant administration of MenACWY, HPV, and Tdap slightly increased the incidence of chills compared to MenACWY alone (MenACWY, 12%; MenACWY + HPV + Tdap, 14%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 12%; Tdap followed 1 month later by MenACWY, 9) did not substantially change the incidence of chills.

Arthralgia

In the total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of arthralgia during the 7 days after vaccination was 9% in the total MenACWY group and 7% in the Menactra group; Table 2.1.1.1.3-1). Severe arthralgia was reported infrequently (1% in each group). The onset of arthralgia was most frequently reported within the first 3 days after vaccination (total MenACWY, 8%;

Menactra, 6%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, arthralgia was reported by 4% in both groups (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of arthralgia following MenACWY alone ranged from 8% to 11% within 7 days after day 1 vaccination (Table 2.1.1.1.4-1), and was less common than Tdap alone. Severe arthralgia was infrequently reported and similar across all vaccine groups (range, 0% to 3%). The incidence of arthralgia in the 19 to 34 year groups (6% and 7%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (6% and 8%) was similar to that seen in the control groups. Severe arthralgia in the 19 to 34 and 35 to 55 year groups was infrequently reported and was similar among the vaccine groups.

As expected when more than one vaccine is administered, the incidence of arthralgia was 11% after MenACWY alone and somewhat higher (16%) after MenACWY given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 11% after MenACWY alone and 17% after MenACWY was given with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 11% after MenACWY alone and 10% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Thus, arthralgia after MenACWY given with concomitant vaccines was worse than MenACWY alone, but sequential administration was no worse in incidence and severity than that observed after MenACWY alone was given. In this case, MenACWY given with concomitant vaccines was more consistent with Tdap results.

In conclusion, concomitant administration of Tdap with MenACWY increased the incidence of arthralgia compared to MenACWY alone in V59P11 (MenACWY alone, 11%; MenACWY + Tdap, 16%) and V59P18 (MenACWY, 11%; MenACWY + HPV + Tdap, 17%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 11%; Tdap followed 1 month later by MenACWY, 10%) did not substantially change the incidence of arthralgia.

Rash

Rash was collected only in studies V59P13, V59P17, and V59P18 (please see CSRs V59P13, V59P17, and V59P18).

In the total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of rash during the 7 days after vaccination was 3% in the total MenACWY group and 2% in the Menactra group; Table 2.1.1.1.3-1). Urticarial rash was reported by 2% of subjects in each vaccines. The onset of rash was consistently reported within the first 3 days and days 4 to 7 after vaccination (total MenACWY, 2%; Menactra, 1%; Appendix 5.3.5.3.2.7 Tables 18 and 22).

In individual studies V59P13 and V59P18 in the 11 to 18 year age group, the incidence of rash following MenACWY alone ranged from 3% to 4% within 7 days after day 1 vaccination (Table 2.1.1.1.4-1). Urticarial and other rash were reported by 1% to 2% of

subjects and by no more than 1% of subjects, respectively. The incidence of rash in the 19 to 34 year groups (3% and 4%; Table 2.1.1.1.4-2) and in the 35 to 55 year groups (2% and 3%) was similar to that seen in the control groups. Urticarial and other rash in the 19 to 34 and 35 to 55 year groups were infrequently reported and were similar in incidence among the vaccine groups.

Rash was not collected in study V59P11, and the comparison of incidence of rash between MenACWY alone and concomitantly with Tdap was not possible (Table 2.1.1.1.4-3). The incidence of rash was 3% after MenACWY alone and was 4% after MenACWY with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3) and was 3% after both MenACWY alone and MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Rash after MenACWY and concomitant or sequential vaccines were given was no worse in incidence than that observed after MenACWY alone was given.

In conclusion, coadministration of licensed concomitant vaccines with MenACWY and sequential administration of Tdap followed by MenACWY alone 1 month later did not change the incidence of rash.

Due to the low incidence of reports of rash, no further comparisons were undertaken.

Fever

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of fever was very low, with more reports in the MenACWY groups than in control groups. However, the incidence of fever exceeding 39°C was 1% or less during the 7 days after vaccination in the total MenACWY group and in the Menactra group; Table 2.1.1.1.3-1). The onset of fever was consistently reported during days 1 to 3 and during days 4 to 7 after vaccination (1% to 2% in both groups; Appendix 5.3.5.3.2.7 Tables 18 and 22).

The incidence of reports of fever exceeding 39°C were 1% or less in comparisons of the effect of concomitant and sequential administration of licensed vaccines, and no further comparisons were undertaken

Other Reactions

Use of Analgesic/Antipyretic Medication

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of analgesic/antipyretic medication use during the 7 days after vaccination was 17% in the total MenACWY group and 19% in the Menactra group; Table 2.1.1.1.3-1). Medication use was most frequently reported within the first 3 days after vaccination (total MenACWY, 13%; Menactra, 14%; Appendix 5.3.5.3.2.7 Table 18); during days 4

to 7, use of analgesic or antipyretic medication was 9% and 10%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of medication use following MenACWY alone ranged from 9% in study V59P11 and 26% in study V59P6 within 7 days after day 1 vaccination (Table 2.1.1.1.4-3), but generally equivalent to the incidence in the control groups. The incidence of analgesic/antipyretic medication use in the 19 to 34 year groups (21% and 17%) and in the 35 to 55 year groups (25% and 14%) was similar to that seen in the control groups.

The incidence of medication use was 9% after MenACWY alone and 11% after MenACWY given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 13% after MenACWY alone and 19% after MenACWY was given with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 13% after MenACWY alone and 10% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). Medication use after MenACWY and concomitant or sequential vaccines were given was no worse in incidence than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY slightly increased the incidence of analgesic/antipyretic medication use compared to MenACWY alone (MenACWY alone, 9%; MenACWY + Tdap, 11%). As expected, concomitant administration of MenACWY, HPV, and Tdap also increased the incidence of medication use compared to MenACWY alone (MenACWY, 13%; MenACWY + HPV + Tdap, 19%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 13%; Tdap followed 1 month later by MenACWY, 10%) slightly reduced the incidence of analgesic/antipyretic medication use.

Stayed Home

In total MenACWY and Menactra comparisons in pooled studies and pooled age groups, the incidence of subjects staying home during the 7 days after vaccination was 4% in both the total MenACWY group and in the Menactra group; Table 2.1.1.1.3-1). Staying home was most frequently reported within the first 3 days after vaccination (total MenACWY, 4%; Menactra, 2%; Appendix 5.3.5.3.2.7 Table 18); during days 4 to 7, staying home was reported by 1% and 2%, respectively (Appendix 5.3.5.3.2.7 Table 22).

In the 11 to 18 year age group in individual studies, the incidence of staying home following MenACWY alone ranged from 3% in study V59P13 to 8% in study V59P18 within 7 days after day 1 vaccination (Table 2.1.1.1.4-3). The incidence of staying home in the 19 to 34 year groups (2% and 5%) and in the 35 to 55 year groups (1% and 5%) was similar to that seen in the 11 to 18 year and control vaccines.

The incidence of staying home was 3% after MenACWY alone and after MenACWY alone given concomitantly with Tdap in study V59P11 (Table 2.1.1.1.4-3), was 8% after

MenACWY alone and 11% after MenACWY was given with concomitant Tdap and HPV in study V59P18 (Table 2.1.1.1.4-3), and was 8% after MenACWY alone and 5% after MenACWY was given sequentially after Tdap in study V59P18 (Table 2.1.1.1.4-4). The incidence of staying home after MenACWY and concomitant or sequential vaccines were given was no worse in incidence than that observed after MenACWY alone was given.

In conclusion, concomitant administration of Tdap with MenACWY did not change the incidence of injection site pain compared to MenACWY alone (MenACWY alone, 3%; MenACWY + Tdap, 3%). Concomitant administration of MenACWY, HPV, and Tdap slightly increased the incidence of staying home compared to MenACWY alone (MenACWY, 8%; MenACWY + HPV + Tdap, 11%). Sequential administration of Tdap followed by MenACWY alone (MenACWY, 8%; Tdap followed 1 month later by MenACWY, 5%) slightly decreased the incidence of staying home.

Overview of Solicited Adverse Events

In summary, review of data on solicited adverse events occurring between days 1 and 7 from the five studies (V59P6, V59P11, V59P13, V59P17, and V59P18) generated the following conclusions:

- Overall reactogenicity rates were similar between MenACWY and Menactra;
- Severe reactions were uncommon with MenACWY;
  - MenACWY appeared slightly more reactogenic than Menactra, particularly among subjects aged 19-34 years;
  - MenACWY was substantially less reactogenic than Tdap;
- There did not appear to be a significant synergistic effect on reactogenicity between MenACWY and a diphtheria-containing vaccine (Tdap);
  - There was no evidence that concomitant vaccination with Tdap or Tdap and HPV increased the reactogenicity of MenACWY;
  - There was no evidence that sequential vaccination with Tdap followed by MenACWY increased the reactogenicity of MenACWY.

2.1.1.2 Unsolicited Adverse Events

For all five studies in the proposed MenACWY indication, unsolicited AEs with first onset or worsening within 29 days after vaccination are presented below (to simplify, this is termed "month 1" or "1 month"), as well as those reported during follow-up from day 30 to study termination (to simplify, this is termed "months 2 to 6"). AEs judged by the investigator to be at least possibly related to the vaccine are also presented.

In pooled studies and pooled age groups, an overview of the percentages of subjects with at least one AE in several categories of unsolicited AEs (any AE, any severe AE, possibly/probably related AE, severe possibly/probably related AE, any SAE, possibly/probably related SAE, and death) is provided in Tables 2.1.1.2.1-1, 2.1.1.2.1-2, and 2.1.1.2.1-3.

Summaries of individual AEs comprising each category of unsolicited AEs are provided in section 2.1.1.2.2.

2.1.1.2.1 Overview of Unsolicited Adverse Events

Total MenACWY Compared With Menactra in Pooled Age Groups and Pooled Studies

During the first month after vaccination with MenACWY or the licensed control vaccines, the incidence of unsolicited AEs was slightly lower for total MenACWY (17% for MenACWY alone combined with MenACWY administered with concomitant licensed vaccines) than for Menactra (20% in Table 2.1.1.2.1-1) pooled across studies and age groups. Any AE that was severe in intensity was reported by 1% in MenACWY and Menactra subjects. Probably or possibly related AEs were reported by 6% and 7% of MenACWY and Menactra subjects, respectively, and related AEs that were severe in intensity were reported by less than 1% of recipients of either vaccine. SAEs were reported by less than 1% of subjects in both groups (seven subjects with SAEs after MenACWY vaccination, none after Menactra) (section 2.1.3). No deaths were reported during the month following vaccination (section 2.1.2).

During months 2 to 6 (study V59P18 was excluded since month 2 to 6 data were not yet available), the incidence of AEs decreased to 9% and 8%, and probably or possibly related AEs to less than 1% for MenACWY and Menactra subjects, respectively (Table 2.1.1.2.1-1). AEs that were severe in intensity remained at 1% for both vaccines, and there were no probably or possibly related AEs that were severe. SAEs were reported by 1% of subjects for both vaccines (31 subjects with SAEs in the MenACWY group, and 10 subjects with SAEs in the Menactra group), and a single possibly related SAE was noted in the MenACWY group (none in Menactra). No deaths were reported during the second through sixth months following vaccination.

The percentage of subjects who experienced at least one unsolicited AE was slightly less after administration of any MenACWY than after Menactra within the first month after vaccination. No clinically meaningful differences were observed during month 2 to month 6 or in the incidence of any severe AE, possibly/probably related AE, severe possibly/probably related AE, any SAE, possibly/probably related SAE, and death at any time in the 11 to 18 year age group.

MenACWY Alone, With Concomitant Vaccines, and Total MenACWY Compared With Menomune, Menactra, and Tdap Vaccines in the 11 to 18 Age Group

During the first month following the vaccination in the 11 to 18 year age group, the percentages of subjects reporting at least one AE in all vaccine groups ranged from 10% to 23% (Table 2.1.1.2.1-2). MenACWY alone and total MenACWY AEs were at 18% and 16% incidence, respectively (MenACWY administered concomitantly with Tdap or Tdap + HPV vaccines in studies V59P11 and V59P18, respectively, were at a combined 13% incidence). Menactra, Menomune, and Tdap were at 20%, 23%, and 10%, respectively). Any AE that was severe in intensity was reported by 1% to 2% of subjects in all vaccine groups, probably or possibly related AEs by 2% to 6%, and related AEs that were severe in intensity by 0% to less than 1%. Six subjects with SAEs were reported (1%) for MenACWY and none by Menactra. None of the MenACWY SAEs was considered probably or possibly related to MenACWY. No deaths were reported during the month following vaccination.

During months 2 to 6 (study V59P18 excluded), the percentages of subjects reporting at least one AE in all vaccine groups ranged from 9% to 15% in the 11 to 18 year age group (Table 2.1.1.2.1-2). MenACWY alone and total MenACWY AEs were both at 11% incidence (MenACWY administered concomitantly with Tdap in study V59P11 was at 12% incidence). Menactra, Menomune, and Tdap were at 9%, 15%, and 10%, respectively). Any AE that was severe in intensity was reported by less than 1% to 5% of subjects in all vaccine groups, probably or possibly related AEs by by a single Menomune subject, and probably or possibly related AEs that were severe in intensity by none of the subjects. Fourteen (1%) total MenACWY subjects reported SAEs (none were vaccine-related). The incidence of subjects reporting SAEs in the comparator groups ranged from less than 1% to 2% (Table 2.1.1.2.1-2).

In conclusion, during the first month after vaccination, the incidence of unsolicited AEs after vaccination with MenACWY alone (18%) and total MenACWY (16%) was less than that noted after Menomune (20%) and Menactra (23%) and greater than that noted after Tdap (10%). MenACWY administered concomitantly with Tdap or Tdap + HPV reduced the incidence of any unsolicited AE (10%) below that noted for other vaccines. No clinically meaningful differences were detected in unsolicited AE or SAE incidence between MenACWY and Menactra in the 11 to 18 year age group.

No clinically meaningful differences were observed during month 2 to month 6 or in the incidence of any other category of unsolicited AE at any time in the 11 to 18 year age group.

MenACWY Compared With Menactra in the 19 to 34 and 35 to 55 Year Groups

During the first month after vaccination, no clinically meaningful differences were detected in the percentages of subjects who reported at least one unsolicited AE between MenACWY alone and Menactra (18% for both vaccines in the 19 to 34 year age group and 20% and 22%, respectively, in the 35 to 55 year age group; Table 2.1.1.2.1-3). Most of the unsolicited AEs for both vaccine groups occurred during the first month after vaccination in both age groups.

No clinically meaningful differences were noted between MenACWY and Menactra in any other category of unsolicited AEs at any time.

Eight percent and 9% of MenACWY subjects in 19 to 34 year and 35 to 55 year age groups, respectively, experienced probably or possibly related AEs during month 1 (Table 2.1.1.2.1-3). One MenACWY subject in the 19 to 34 year age group and none of the subjects in the 35 to 55 year group experienced at least one unrelated SAE during month 1. These results were similar with those noted for the Menactra group during month 1.

During months 2 to 6, less than 1% of the MenACWY subjects in both age groups experienced related AEs (Table 2.1.1.2.1-3). Eleven and seven MenACWY subjects in 19 to 34 year and 35 to 55 year age groups, respectively, experienced at least one SAE; one of these SAEs was considered possibly related to study vaccine. These results were also similar with those for the Menactra group.

Table 2.1.1.2.1-1 Overview of Unsolicited Adverse Events: Comparing Total ACWY to Menactra in Pooled Studies and Pooled Age Groups

Time	Overview of Unsolicited Adverse Events (AE)	Total MenACWY N or n (%)	Menactra N or n (%)
Month 1	**Total exposed: N**	**6185**	**1757**
	Any AE	1076 (17)	356 (20)
	Any severe AE	59 (1)	16 (1)
	Possibly/probably related AE	357 (6)	128 (7)
	Severe possibly/probably related AE	21 (<1)	5 (<1)
	Any SAE	7 (<1)	4 (<1)
	Possibly/probably related SAE	0	0
	Death	0	0
Months 2 to 6	**Total exposed: N** [a]	**5068**	**1746**
	Any AE	460 (9)	134 (8)
	Any severe AE	42 (1)	14 (1)
	Possibly/probably related AE	3 (<1)	1 (<1)
	Severe possibly/probably related AE	0	0
	Any SAE	31 (1)	10 (1)
	Possibly/probably related SAE	1 (<1)	0
	Death	0	0

Appendix 5.3.5.3.2.7: Month 1, Tables 32, 37, 43, 49, 67, 71, and 75; months 2 to 6, Tables 35, 39, 47, 51, 67, and 73.
N = subjects with at least one event.
[a] Study V59P18 (CSR V59P18 section 5.3.5.1.16) excluded; study is ongoing: data for the complete 2 to 6 month period are not yet available.

Table 2.1.1.2.1-2 Overview of Unsolicited Adverse Events: Comparing MenACWY With Other Vaccine Groups Within the 11 to 18 Age Group in Pooled Studies

Time	Overview of Unsolicited Adverse Events (AE)	MenACWY Alone [a]	MenACWY+ ConVax [b]	Total ACWY [c]	Menactra [d]	Menomune [e]	Tdap [f]
Month 1	**Total exposed: N**	**2680**	**899**	**3579**	**539**	**209**	**892**
	Any AE	472 (18)	114 (13)	586 (16)	109 (20)	49 (23)	93 (10)
	Any severe AE	24 (1)	5 (1)	29 (1)	5 (1)	4 (2)	6 (1)
	Possibly/probably related AE	110 (4)	31 (3)	141 (4)	33 (6)	4 (2)	28 (3)
	Severe possibly/probably related E	5 (<1)	2 (<1)	7 (<1)	1 (<1)	0	2 (<1)
	Any SAE	5 (<1)	1 (<1)	6 (<1)	0	0	0
	Possibly/probably related SAE	0	0	0	0	0	0
	Death	0	0	0	0	0	0
Months 2 to 6 [g]	**Total exposed: N**	**2139**	**359**	**2498**	**539**	**209**	**353**
	Any AE	227 (11)	42 (12)	269 (11)	48 (9)	31 (15)	36 (10)
	Any severe AE	22 (1)	1 (<1)	23 (1)	5 (1)	10 (5)	1 (<1)
	Possibly/probably related AE	0	0	0	0	1 (<1)	0
	Severe possibly/probably related AE	0	0	0	0	0	0
	Any SAE	13 (1)	1 <1)	14 (1)	2 (<1)	5 (2)	2 (<1)
	Possibly/probably related SAE	0	0	0	0	0	0
	Death	0	0	0	0	0	0

Appendix 5.3.5.3.2.7: Month 1, Tables 33.1, 38.1, 44.1, 50.1, 67, and 72.1; months 2 to 6, Tables 36.1, 40.1, 48.1, 52.1, 67, 74.1, and 76.1. [a] MenACWY Alone from studies V59P6, P11, P13, P17, and P18. [b] MenACWY + concomitant vaccines from studies V59P11 (MenACWY + Tdap) and P18 (Tdap + MenACWY + HPV). [c] Total MenACWY = MenACWY Alone (footnote [a]) + MenACWY + concomitant vaccines (footnote [b]). [d] Menactra from study V59P13 only. [e] Menomune from study V59P6 only. [f] Tdap from study V59P11 and first month of P18 (Tdap followed 31 days later by MenACWY). [g] Study V59P18 is excluded from this time period. Note: Cell entries are N or n (%).

Table 2.1.1.2.1-3 Overview of Unsolicited Adverse Events: Comparing MenACWY Alone to Menactra Within 19 to 34 and 35 to 55 Age Groups

Time	Overview of Unsolicited Adverse Events (AE)	19 to 34 Age Group		35 to 55 Age Group	
		MenACWY Alone	Menactra	MenACWY Alone	Menactra
Month 1	**N exposed**	**1145**	**569**	**1461**	**649**
	Any AE	205 (18)	101 (18)	285 (20)	146 (22)
	Any severe AE	12 (1)	3 (1)	18 (1)	8 (1)
	Possibly/probably related AE	86 (8)	38 (7)	130 (9)	57 (9)
	Severe possibly/probably related AE	5 (<1)	1 <1)	9 (1)	3 (<1)
	Any SAE	1 (<1)	2 (<1)	0	2 (<1)
	Possibly/probably related SAE [a]	0	0	0	0
	Death	0	0	0	0
Months 2 to 6	**N exposed**	**1145**	**569**	**1461**	**649**
	Any AE	76 (7)	40 (7)	115 (8)	47 (7)
	Any severe AE	9 (1)	3 (1)	10 (1)	6 (1)
	Possibly/probably related AE	2 (<1)	1 (<1)	1 (<1)	0
	Severe possibly/probably related AE	0	0	0	0
	Any SAE	10 (1)	4 (1)	7 (<1)	4 (1)
	Possibly/probably related SAE [a]	1 (<1)	0	0	0
	Death	0	0	0	0

Appendix 5.3.5.3.2.7: Month 1, Tables 33.2 and 33.3, 38.2 and 38.3, 44.2 and 44.3, 50.2 and 50.3, 67, 72.2 and 72.3, and 76.2; months 2 to 6, Tables 36.2 and 36.3, 40.2 and 40.3, 48.2 and 48.3, 52.2 and 52.3, 67, 74.2 and 74.3, and 76.3. Note: Cell entries are N or n (%).
a Timing of SAEs based on Appendix 5.3.5.3.2.7 Table 68.

2.1.1.2.2 Summary of Unsolicited Adverse Events

An overview of the percentages of subjects with at least one unsolicited AE in several categories of unsolicited AEs is provided in Tables 2.1.1.2.1-1, 2.1.1.2.1-2, and 2.1.1.2.1-3.

Summaries of individual AEs comprising each category of unsolicited AEs (any AE, any severe AE, possibly/probably related AE, severe possibly/probably related AE, any SAE, possibly/probably related SAE, and death) are provided in following sections.

2.1.1.2.2.1 All Unsolicited Adverse Events

Most Frequent Unsolicited Adverse Events: Total MenACWY Compared With Menactra

During month 1 after the vaccination, headache was the only AE that occurred with an incidence of 1% or more in the total MenACWY group (Appendix 5.3.5.3.2.7 Table 30; see also Table 32.1 for a complete listing of total MenACWY and Menactra AEs). No clinically meaningful difference in the incidence of headache was noted between the total MenACWY and Menactra groups (2% each).

During months 2 to 6 (study V59P18 excluded), none of the AEs was reported by 1% or more of the subjects (Appendix 5.3.5.3.2.7 Table 31).

MenACWY Alone, With Concomitant Vaccines, and Total MenACWY Compared With Menomune, Menactra, and Tdap Vaccines Within Each Age Group

Thirty Minutes After Vaccination

There were no episodes of anaphylaxis or immediate hypersensitivity within 30 minutes after vaccination. Seventeen of 5219 subjects (less than 1%) in the 11 to 18 year age group in the five vaccine groups (MenACWY, MenACWY + concomitant vaccine, Menactra, Menomune, and Tdap; Appendix 5.3.5.3.2.7 Table 34.1) reported at least one AE within 30 minutes after vaccination; all of these AEs were reported by less than 1% of the subjects in any group. In the 19 to 34 and 35 to 55 year age groups, 15 of 1714 subjects and 9 of 2110 subjects reported at least one AE (Tables 34.2 and 34.3, respectively); all of the AEs were reported by less than 1% of the subjects.

One Month After Vaccination

Within 1 month after vaccination, 837 subjects in the 11 to 18 year age group reported at least one AE in the five vaccine groups (Table 2.1.1.2.2.1-1). There were no clinically meaningful differences among the vaccine groups in the 11 to 18 year age group in the incidence of any AE. The most frequently reported AEs reported by the total MenACWY group were headache (2% incidence) and pharyngolaryngeal pain, dysmenorrhea, upper

respiratory tract infection, cough, nausea, malaise, pharyngitis, and vomiting (all 1%). The incidence of unsolicited AEs after MenACWY was not increased by concomitant administration of MenACWY and Tdap or Tdap + HPV. The most frequent Menactra AE was headache (2%), and the most frequent Menomune AEs were headache (4%), pharyngolaryngeal pain (3%), and cough, malaise, and pharyngitis (all 2%). For the Tdap group, the most frequently reported AE was also headache (2%).

In the 19 to 34 year and 35 to 55 year age groups, there were also no clinically meaningful differences between MenACWY alone and Menactra in the incidence of any AE (Table 2.1.1.2.2.1-2). Headache was reported by the largest percentage of subjects in both age groups (3% in the 19 to 34 group, and 2% in the 35 to 55 group).

Two to Six Months After Vaccination

Between 2 and 6 months after vaccination (study V59P18 excluded), there were no clinically meaningful differences among the vaccine groups in 11 to 18, 19 to 34, and 35 to 55 year age groups (Tables 2.1.1.2.2.1-3 and Table 2.1.1.2.2.1-4). In 11 to 18 year subjects, percentages of MenACWY alone and total MenACWY subjects who reported individual AEs at least once in the infections and infestations system organ class did not exceed 1%. Pharyngitis, influenza, headache, and pyrexia were reported by 3%, 2%, 2%, and 2%, respectively, of MenACWY + concomitant vaccine subjects. Pharyngitis and influenza were reported by 3% and 2% of Tdap subjects. AEs reported by Menactra and Menomune subjects did not exceed 1%.

In 19 to 34 and 35 to 55 year age groups, AEs were reported by less than 1% of the subjects (Table 2.1.1.2.2.1-4), and there were no clinically meaningful differences in AE incidence between the vaccine groups.

Table 2.1.1.2.2.1-1 Summary of Unsolicited Adverse Events Within 1 Month After Vaccination: Comparing Treatments Within 11 to 18 Age Group

Unsolicited Adverse Event: MedDRA Preferred Term	MenACWY Alone [a] N=2680	MenACWY+ ConVax [b] N=899	Total ACWY [c] N=3579	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=892
Headache	44 (2)	14 (2)	58 (2)	9 (2)	9 (4)	16 (2)
Pharyngolaryngeal pain	31 (1)	1 (<1)	32 (1)	8 (1)	6 (3)	2 (<1)
Dysmenorrhea	17 (1)	13 (1)	30 (1)	0	2 (1)	6 (1)
Upper respiratory tract infection	19 (1)	10 (1)	29 (1)	7 (1)	3 (1)	2 (<1)
Cough	21 (1)	5 (1)	26 (1)	1 (<1)	4 (2)	3 (<1)
Nausea	22 (1)	3 (<1)	25 (1)	2 (<1)	2 (1)	5 (1)
Malaise	19 (1)	5 (1)	24 (1)	3 (1)	4 (2)	6 (1)
Pharyngitis	13 (<1)	7 (1)	20 (1)	0	5 (2)	2 (<1)
Vomiting	16 (1)	2 (<1)	18 (1)	4 (1)	3 (1)	2 (<1)
Nasopharyngitis	10 (<1)	7 (1)	17 (<1)	3 (1)	3 (1)	5 (1)
Pyrexia	9 (<1)	8 (1)	17 (<1)	0	1 (<1)	7 (1)
Diarrhoea	12 (<1)	4 (<1)	16 (<1)	7 (1)	0	1 (<1)
Abdominal pain upper	12 (<1)	4 (<1)	16 (<1)	2 (<1)	0	1 (<1)
Nasal congestion	15 (1)	0	15 (<1)	4 (1)	3 (1)	1 (<1)
Arthralgia	13 (<1)	1 (<1)	14 (<1)	3 (1)	0	2 (<1)
Sinusitis	13 (<1)	0	13 (<1)	1 (<1)	2 (1)	2 (<1)

Unsolicited Adverse Event: MedDRA Preferred Term	MenACWY Alone [a] N=2680	MenACWY+ ConVax [b] N=899	Total ACWY [c] N=3579	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=892
Dermatitis contact	12 (<1)	0	12 (<1)	3 (1)	0	0
Myalgia	11 (<1)	0	11 (<1)	2 (<1)	1 (<1)	5 (1)
Abdominal pain	6 (<1)	5 (1)	11 (<1)	1 (<1)	0	6 (1)
Injection site pruritis	11 (<1)	0	11 (<1)	1 (<1)	0	0
Injection site erythema	10 (<1)	1 (<1)	11 (<1)	1 (<1)	0	1 (<1)
Rash	8 (<1)	2 (<1)	10 (<1)	2 (<1)	0	0
Pharyngitis streptococcal	10 (<1)	0	10 (<1)	2 (<1)	1 (<1)	0
Pain in extremity	7 (<1)	2 (<1)	9 (<1)	4 (1)	1 (<1)	0
Joint sprain	9 (<1)	0	9 (<1)	2 (<1)	0	1 (<1)
Injection site induration	7 (<1)	2 (<1)	9 (<1)	0	0	2 (<1)
Toothache	6 (<1)	3 (<1)	9 (<1)	1 (<1)	0	0
Pain	5 (<1)	3 (<1)	8 (<1)	0	0	1 (<1)
Tonsillitis	4 (<1)	4 (<1)	8 (<1)	0	0	4 (<1)
Rhinorrhoea	7 (<1)	0	7 (<1)	1 (<1)	0	0
Sinus congestion	7 (<1)	0	7 (<1)	0	0	0
Influenza	5 (<1)	2 (<1)	7 (<1)	0	1 (<1)	3 (<1)
Dizziness	5 (<1)	2 (<1)	7 (<1)	3 (1)	1 (<1)	2 (<1)
Back pain	6 (<1)	1 (<1)	7 (<1)	0	0	1 (<1)

Unsolicited Adverse Event: MedDRA Preferred Term	MenACWY Alone [a] N=2680	MenACWY+ ConVax [b] N=899	Total ACWY [c] N=3579	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=892
Erythema	4 (<1)	2 (<1)	6 (<1)	1 (<1)	0	0
Chills	6 (<1)	0	6 (<1)	0	1 (<1)	2 (<1)
Injection site pain	6 (<1)	0	6 (<1)	2 (<1)	0	1 (<1)
Lymphadenopathy	6 (<1)	0	6 (<1)	0	0	2 (<1)
Adnexa uteri pain	2 (<1)	3 (<1)	5 (<1)	0	0	1 (<1)
Ear pain	4 (<1)	1 (<1)	5 (<1)	1 (<1)	1 (<1)	1 (<1)
Injection site swelling	5 (<1)	0	5 (<1)	0	0	1 (<1)
Arthropod bite	4 (<1)	1 (<1)	5 (<1)	0	0	0
Excoriation	5 (<1)	0	5 (<1)	1 (<1)	0	0

Appendix 5.3.5.3.2.7 Table 33.1. Criterion for inclusion in this table = 5 subjects or more in total ACWY group. Cell entries are n (%).
a MenACWY Alone from studies V59P6, P11, P13, P17, and P18.
b MenACWY + concomitant vaccines from studies V59P11 (MenACWY + Tdap) and P18 (Tdap + MenACWY + HPV).
c Total MenACWY (footnote c) = MenACWY Alone (footnote a) + MenACWY + concomitant vaccines (footnote b).
d Menactra from study V59P13 only.
e Menomune from study V59P6 only.
f Tdap from study V59P11 and first 29 days of P18.

Table 2.1.1.2.2.1-2 Summary of Unsolicited Adverse Events Within 1 Month After Vaccination: Comparing MenACWY and Menactra Within 19 to 34 and 35 to 55 Age Groups

Unsolicited Adverse Event: MedDRA Preferred Term	19 to 34 Age Group		35 to 55 Age Group	
	MenACWY Alone N=1145	Menactra N=569	MenACWY Alone N=1461	Menactra N=649
Headache	29 (3)	12 (2)	31 (2)	16 (2)
Malaise	16 (1)	3 (1)	18 (1)	4 (1)
Myalgia	8 (1)	4 (1)	17 (1)	6 (1)
Nasopharyngitis	17 (1)	6 (1)	13 (1)	6 (1)
Back pain	6 (1)	4 (1)	16 (1)	6 (1)
Arthralgia	7 (1)	2 (<1)	15 (1)	11 (2)
Injection site pain	9 (1)	1 (<1)	13 (1)	5 (1)
Dysmenorrhoea	13 (1)	3 (1)	6 (<1)	2 (<1)
Pharyngolaryngeal pain	7 (1)	3 (1)	12 (1)	4 (1)
Nausea	12 (1)	4 (1)	3 (<1)	1 (<1)
Diarrhoea	12 (1)	6 (1)	9 (1)	4 (1)
Injection site erythema	12 (1)	0	9 (1)	1 (<1)
Injection site pruritis	4 (<1)	3 (1)	12 (1)	1 (<1)
Lymphadenopathy	3 (<1)	2 (<1)	9 (1)	1 (<1)
Rhinitis	2 (<1)	2 (<1)	9 (1)	3 (<1)
Pain in extremity	2 (<1)	1 (<1)	9 (1)	10 (2)
Erythema	1 (<1)	2 (<1)	9 (1)	1 (<1)
Dizziness	8 (1)	4 (1)	6 (<1)	9 (1)

Unsolicited Adverse Event: MedDRA Preferred Term	19 to 34 Age Group		35 to 55 Age Group	
	MenACWY Alone N=1145	Menactra N=569	MenACWY Alone N=1461	Menactra N=649
Urinary tract infection	1 (<1)	3 (1)	7 (<1)	3 (<1)
Pharyngitis	3 (<1)	4 (1)	7 (<1)	1 (<1)
Injection site induration	6 (1)	1 (<1)	6 (<1)	0
Sinus headache	1 (<1)	0	6 (<1)	1 (<1)
Rash	4 (<1)	0	6 (<1)	4 (1)
Fatigue	3 (<1)	0	6 (<1)	1 (<1)
Dyspepsia	2 (<1)	1 (<1)	6 (<1)	2 (<1)
Viral infection	3 (<1)	0	6 (<1)	1 (<1)
Migraine	6 (1)	0	3 (<1)	0
Chills	3 (<1)	1 (<1)	6 (<1)	1 (<1)
Abdominal pain	6 (1)	7 (1)	4 (<1)	4 (1)
Abdominal pain upper	6 (1)	0	2 (<1)	1 (<1)
Influenza-like illness	5 (<1)	1 (<1)	5 (<1)	2 (<1)
Induration	1 (<1)	1 (<1)	5 (1)	0
Neck pain	2 (<1)	1 (<1)	5 (<1)	0
Vomiting	1 (<1)	3 (1)	5 (<1)	2 (<1)

Appendix 5.3.5.3.2.7 Table 33.2, 33.3. Criterion for inclusion in this table = 5 subjects or more in ACWY alone group. Cell entries are n (%).
Ordered by decreasing frequency of MenACWY alone group in either 19 to 34 year age group or 35 to 55 year age group, whichever is greater for the AE.

Table 2.1.1.2.2.1-3 Summary of Unsolicited Adverse Events Within 2 to 6 Months After Vaccination: Comparing Treatments Within 11 to 18 Age Group (Study V59P18 Excluded)

Unsolicited Adverse Events		MenACWY Alone [a] N=2139	MenACWY+ ConVax [b] N=359	Total ACWY [c] N=2498	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=353
MedDRA System Organ Class	MedDRA Preferred Term						
Any AE		227 (11)	42 (12)	269 (11)	48 (9)	31 (15)	36 (10)
Gastrointestinal disorders	**Diarrhoea**	5 (<1)	2 (1)	7 (<1)	0	0	3 (1)
	Vomiting	4 (<1)	1 (<1)	5 (<1)	0	0	3 (1)
General disorders & administration site conditions	**Pyrexia**	2 (<1)	8 (2)	10 (<1)	0	1 (<1)	3 (1)
Infections & infestations	**Bronchitis**	3 (<1)	3 (1)	6 (<1)	0	0	0
	Gastroenteritis	2 (<1)	3 (1)	5 (<1)	0	1 (<1)	1 (<1)
	Influenza	9 (<1)	8 (2)	17 (1)	0	1 (<1)	7 (2)
	Nasopharyngitis	2 (<1)	5 (1)	7 (<1)	0	0	2 (1)
	Pharyngitis	9 (<1)	9 (3)	18 (1)	0	1 (<1)	10 (3)
	Tonsillitis	4 (<1)	2 (1)	6 (<1)	0	0	3 (1)
Injury & poisoning	**Contusion**	8 (<1)	0	8 (<1)	1 (<1)	1 (<1)	1 (<1)
	Foot fracture	6 (<1)	0	6 (<1)	1 (<1)	0	0
	Hand fracture	5 (<1)	0	5 (<1)	1 (<1)	1 (<1)	0
	Joint sprain	5 (<1)	0	5 (<1)	1 (<1)	2 (1)	0
	Limb injury	6 (<1)	0	6 (<1)	1 (<1)	0	0

Unsolicited Adverse Events		MenACWY Alone [a] N=2139	MenACWY+ ConVax [b] N=359	Total ACWY [c] N=2498	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=353
MedDRA System Organ Class	**MedDRA Preferred Term**						
Musculoskeletal, connective tissue & bone disorders	**Arthralgia**	8 (<1)	0	8 (<1)	4 (1)	0	1 (<1)
Nervous system disorders	**Headache**	6 (<1)	6 (2)	12 (<1)	1 (<1)	1 (<1)	2 (1)
Psychiatric disorders	**Depression**	6 (<1)	0	6 (<1)	2 (<1)	3 (1)	0
Respiratory, thoracic & mediastinal disorders	**Rhinitis allergic**	7 (<1)	0	7 (<1)	1 (<1)	0	0

Appendix 5.3.5.3.2.7 Table 36.1. Criterion for inclusion in this table = 5 subjects or more in total ACWY group. Cell entries are n (%).
[a] MenACWY Alone from studies V59P6, P11, P13, and P17. Study V59P18 is excluded from this time period.
[b] MenACWY + concomitant vaccines from study V59P11 (MenACWY + Tdap). Study V59P18 (Tdap + MenACWY + HPV) is excluded from this time period.
[c] Total MenACWY (footnote [c]) = MenACWY Alone (footnote [a]) + MenACWY + concomitant vaccines (footnote [b]).
[d] Menactra from study V59P13 only.
[e] Menomune from study V59P6 only.
[f] Tdap from study V59P11.

Table 2.1.1.2.2.1-4 Summary of Unsolicited Adverse Events Within 2 to 6 Months After Vaccination: Comparing MenACWY and Menactra Within 19 to 34 and 35 to 55 Age Groups

Unsolicited Adverse Events		19 to 34 Age Group		35 to 55 Age Group	
MedDRA System Organ Class	**MedDRA Preferred Term**	**MenACWY Alone N=1145**	**|Menactra N=569**	**MenACWY Alone N=1461**	**Menactra N=649**
Any AE		76 (7)	40 (7)	115 (8)	47 (7)
Gastrointestinal disorders	**Gastritis**	5 (<1)	0	5 (<1)	3 (<1)
Infections & infestations	**Bronchitis**	5 (<1)	1 (<1)	4 (<1)	0
	Pneumonia	4 (<1)	0	5 (<1)	0
Injury & poisoning	**Injury**	1 (<1)	1 (<1)	7 (<1)	1 (<1)

Appendix 5.3.5.3.2.7 Tables 36.2, 36.3. Criterion for inclusion in this table = 5 subjects or more in MenACWY groups. Cell entries are n (%).

2.1.1.2.2.2 All Severe Unsolicited Adverse Events

Most Frequent Severe Unsolicited Adverse Events: Total MenACWY Compared With Menactra

During the first month after vaccination, none of the severe AEs in total MenACWY subjects were reported at an incidence that exceeded 1% (Table 2.1.1.2.2.2-1). No clinically meaningful differences in the incidence of any severe AE were noted between the total MenACWY and Menactra groups. The most frequently reported severe AEs in the total MenACWY groups were headache, malaise, and nausea, which was consistent with reactogenicity results.

During months 2 to 6 (study V59P18 excluded), all severe AEs were reported at an incidence of less than 1% (Appendix 5.3.5.3.2.7 Table 39). The severe AEs reported in more than one subject in total MenACWY groups were pneumonia, appendicitis, clavical fracture, ligament rupture, road traffic accident, spontaneous abortion, and suicide attempt. There were no clinically meaningful differences between total MenACWY and Menactra groups in the incidence of any severe AE.

All Severe Unsolicited Adverse Events After MenACWY Alone, With Concomitant Vaccines, and Total MenACWY Compared With Menomune, Menactra, and Tdap Vaccines Within Each Age Group

None of the severe AEs reported by MenACWY or comparator subjects exceeded 1% incidence at 1 month or 2 to 6 months (study V59P18 excluded) after vaccination in 11 to 18, 19 to 34, or 35 to 55 year groups (Appendix 5.3.5.3.2.7 Tables 38.1, 38.2, 38.3, 40.1, 40.2, and 40.3).

Table 2.1.1.2.2.2-1 Summary of Severe Unsolicited Adverse Events Within One Month After Vaccination: Total MenACWY Compared With Menactra in Pooled Studies

Unsolicited Adverse Events		Total MenACWY N=6185	Menactra N=1757
MedDRA System Organ Class	MedDRA Preferred Term		
Any severe AE		59 (1)	16 (1)
Gastrointestinal disorders	Nausea	5 (<1)	1 (<1)
General disorders & administration site conditions	Injection site pain	3 (<1)	0
	Malaise	6 (<1)	1 (<1)
Infections & infestations	Pharyngitis streptococcal	2 (<1)	0
Musculoskeletal, connective tissue & bone disorders	Arthralgia	3 (<1)	2 (<1)
	Myalgia	3 (<1)	1 (<1)
Nervous system disorders	Headache	14 (<1)	4 (<1)
	Migraine	3 (<1)	1 (<1)
Psychiatric disorders	Depression	3 (<1)	0

Appendix 5.3.5.3.2.7 Table 37. Criterion for inclusion in this table = 2 or more subjects in the total MenACWY group. Cell entries are n (%).
[a]Total exposed to vaccine.
Note: Study V59P18 is excluded from this time period.

2.1.1.2.2.3 All Probably or Possibly Related Unsolicited Adverse Events

Most Frequent Probably or Possibly Related Unsolicited Adverse Events: Total MenACWY Compared With Menactra

During the first month after vaccination, none of the probably to possibly related AEs in total MenACWY subjects was reported at an incidence that exceeded 1% (Table 2.1.1.2.2.3-1). No clinically meaningful differences in the incidence of any related AE were noted in month 1 between the total MenACWY and Menactra groups. The most frequently reported, related AEs in the total MenACWY groups were headache, malaise, and injection site erythema (all 1% incidence). All other related AEs were reported at an incidence of less than 1%.

During months 2 to 6 (study V59P18 excluded), only four related AEs were reported by total MenACWY subjects, and all events were reported by only one subject (Appendix 5.3.5.3.2.7 Table 42). There were no clinically meaningful differences between total

MenACWY and Menactra groups in the incidence of any related AE during months 2 to 6.

Table 2.1.1.2.2.3-1 Summary of Probably or Possibly Related Unsolicited Adverse Events Within 1 Month After Vaccination: Total MenACWY Compared With Menactra in Pooled Age Groups and Pooled Studies and Sorted by Descending Frequency

Unsolicited Adverse Events: MedDRA Preferred Term	Total MenACWY N=6185	Menactra N=1757
Headache	62 (1)	20 (1)
Malaise	34 (1)	5 (<1)
Injection site erythema	32 (1)	2 (<1)
Injection site pain	28 (<1)	8 (<1)
Injection site pruritis	25 (<1)	5 (<1)
Myalgia	23 (<1)	7 (<1)
Nausea	23 (<1)	3 (<1)
Injection site induration	21 (<1)	1 (<1)
Arthralgia	18 (<1)	11 (1)
Erythema	14 (<1)	4 (<1)
Diarrhoea	13 (<1)	5 (<1)
Lymphadenopathy	13 (<1)	2 (<1)
Rash	13 (<1)	5 (<1)
Nasopharyngitis	12 (<1)	5 (<1)
Dizziness	10 (<1)	12 (1)
Pharyngolaryngeal pain	10 (<1)	5 (<1)
Induration	10 (<1)	2 (<1)

Appendix 5.3.5.3.2.7 Table 41. Criterion for inclusion in this table = 10 subjects in the total ACWY group. Cell entries are n (%).

All Probably or Possibly Related Unsolicited Adverse Events After MenACWY Alone, With Concomitant Vaccines, and Total MenACWY Compared With Menomune, Menactra, and Tdap Vaccines Within Each Age Group

In the 11 to 18 year age group, the incidence of any probably or possibly related unsolicited AE within 1 month after vaccination was 4%, 6%, 2%, and 3% in the total MenACWY, Menactra, Menomune, and Tdap groups, respectively. During the first month after vaccination, at least one probably or possibly related headache was reported by total MenACWY subjects (1% incidence in 11 to 18 and 35 to 55 year age groups and

2% in 19 to 34 year age groups (Tables 2.1.1.2.2.3-2 and 2.1.1.2.2.3-3). There were no clinically meaningful differences between total MenACWY and comparator vaccine groups in the incidence of any related AE within the first month following vaccination.

Appendix 5.3.5.3.2.7 Tables 45.1, 45.2, and 45.3 show that nearly all related AEs were reported during days 1 through 7 after vaccination and that few related AEs were reported during days 8 to 29 (Appendix 5.3.5.3.2.7 Tables 46.1, 46.2, and 46.3).

During days 1 to 7, 1% of total MenACWY 11 to 18 year age groups reported at least one related headache, and 2% and 1% of 19 to 34 and 35 to 55 year age groups, respectively, reported related headache (Appendix 5.3.5.3.2.7 Tables 45.1, 45.2, and 45.3).

During days 8 to 29, related AEs were rare in all three age groups and occurred at an incidence of less than 1% (Appendix 5.3.5.3.2.7 Tables 46.1, 46.2, and 46.3).

During months 2 to 6 (study V59P18 excluded), related AEs were also rarely reported by subjects in all three age groups (incidence less than 1%; Appendix 5.3.5.3.2.7 Tables 48.1, 48.2, and 48.3).

Table 2.1.1.2.2.3-2 Summary of Probably or Possibly Related Unsolicited Adverse Events Within 1 Month After Vaccination: Comparing Total MenACWY Within 11 to 18 Age Group

Unsolicited Adverse Events		MenACWY Alone [a] N=2680	MenACWY+ ConVax [b] N=899	Total ACWY [c] N=3579	Menactra [d] N=539	Menomune [e] N=209	Tdap [f] N=892
MedDRA System Organ Class	**MedDRA Preferred Term**						
Any probably or possibly related AE		110 (4)	31 (3)	141 (4)	33 (6)	4 (2)	28 (3)
Gastrointestinal disorders	**Nausea**	10 (<1)	2 (<1)	12 (<1)	1 (<1)	0	4 (<1)
General disorders & administration site conditions	**Injection site erythema**	10 (<1)	1 (<1)	11 (<1)	1 (<1)	0	1 (<1)
	Injection site induration	7 (<1)	2 (<1)	9 (<1)	0	0	2 (<1)
	Injection site pain	6 (<1)	0	6 (<1)	2 (<1)	0	1 (<1)
	Injection site pruritis	10 (<1)	0	10 (<1)	1 (<1)	0	0
	Injection site swelling	5 (<1)	0	5 (<1)	0	0	1 (<1)
	Malaise	9 (<1)	3 (<1)	12 (<1)	2	1 (<1)	6 (1)
	Pain	4 (<1)	3 (<1)	7 (<1)	0	0	1 (<1)
Musculoskeletal, connective tissue & bone disease	**Arthralgia**	5 (<1)	1 (<1)	6 (<1)	2 (<1)	0	2 (<1)
	Myalgia	7 (<1)	0	7 (<1)	2 (<1)	1 (<1)	5 (1)
	Pain in extremity	3 (<1)	2 (<1)	5 (<1)	1 (<1)	1 (<1)	0
Nervous system disorders	**Headache**	13 (<1)	11 (1)	24 (1)	3 (1)	0	11 (1)
Skin & subcutaneous tissue disorders	**Erythema**	3 (<1)	2 (<1)	5 (<1)	1 (<1)	0	0

Appendix 5.3.5.3.2.7 Table 44.1. Criterion for inclusion in this table = at least 5 subjects in the total MenACWY group. Cell entries are n (%). [a] MenACWY Alone from studies V59P6, P11, P13, P17, and P18. [b] MenACWY + concomitant vaccines from studies V59P11 (MenACWY + Tdap) and P18 (Tdap + MenACWY + HPV). [c] Total MenACWY (footnote c) = MenACWY Alone (footnote a) + MenACWY + concomitant vaccines (footnote b). [d] Menactra from study V59P13 only. [e] Menomune from study V59P6 only. [f] Tdap from study V59P11 and first 30 days of P18.

Table 2.1.1.2.2.3-3 Summary of Probably or Possibly Related Unsolicited Adverse Events Within 1 Month After Vaccination: Comparing Total MenACWY and Menactra Within 19 to 34 and 35 to 55 Age Groups

Unsolicited Adverse Events		19 to 34 Age Group		35 to 55 Age Group	
MedDRA System Organ Class	MedDRA Preferred Term	MenACWY Alone N=1145	Menactra N=569	MenACWY Alone N=1461	Menactra N=649
Any probably or possibly related AE		86 (8)	38 (7)	130 (9)	57 (9)
Blood & lymphatic system disorders	**Lymphadenopathy**	3 (<1)	2 (<1)	7 (<1)	0
Gastrointestinal disorders	**Diarrhoea**	7 (1)	1 (<1)	2 (<1)	2 (<1)
	Nausea	8 (1)	2 (<1)	3 (<1)	0
General disorders & administrative site conditions	**Fatigue**	2 (<1)	0	6 (<1)	1 (<1)
	Induration	1 (<1)	1 (<1)	5 (<1)	0
	Injection site erythema	12 (1)	0	9 (1)	1 (<1)
	Injection site induration	6 (1)	1 (<1)	6 (<1)	0
	Injection site pain	9 (1)	1 (<1)	13 (1)	5 (1)
	Injection site pruritis	3 (<1)	3 (1)	12 (1)	1 (<1)
	Malaise	8 (1)	1 (<1)	14 (1)	2 (<1)
Infections & infestations	**Nasopharyngitis**	4 (<1)	2 (<1)	6 (<1)	2 (<1)
Musculoskeletal, connective tissue & bone disorders	**Arthralgia**	4 (<1)	2 (<1)	8 (1)	7 (1)
	Back pain	2 (<1)	1 (<1)	6 (<1)	0
	Myalgia	3 (<1)	2 (<1)	13 (1)	3 (<1)
Nervous system disorders	**Dizziness**	6 (1)	2 (<1)	4 (<1)	8 (1)
	Headache	18 (2)	7 (1)	20 (1)	10 (2)

Unsolicited Adverse Events		19 to 34 Age Group		35 to 55 Age Group	
MedDRA System Organ Class	**MedDRA Preferred Term**	**MenACWY Alone N=1145**	**Menactra N=569**	**MenACWY Alone N=1461**	**Menactra N=649**
Respiratory, thoracic & mediastinal disorders	**Pharynlaryngeal pain**	0	1 (<1)	6 (<1)	2 (<1)
Skin & subcutaneous disorders	**Erythema**	1 (<1)	2 (<1)	8 (1)	1 (<1)
	Rash	4 (<1)	0	6 (<1)	3 (<1)

Appendix 5.3.5.3.2.7 Tables 44.2 and 44.3. Criterion for inclusion in this table = at least 5 subjects in the total MenACWY group. Cell entries are n (%).

2.1.1.2.2.4 All Severe, Probably or Possibly Related Unsolicited Adverse Events

Most Frequent Severe Probably or Possibly Related Unsolicited Adverse Events: Total MenACWY Compared With Menactra

Less than 1% of total MenACWY and Menactra subjects reported at least one severe, probably or possibly related unsolicited AE during month 1 (Appendix 5.3.5.3.2.7 Table 49). Headache, nausea, and malaise were most frequent in the total MenACWY group, and headache was most frequent in the Menactra group. There were no clinically meaningful differences between the two groups in any severe probably or possibly related AE.

No such AEs were reported during months 2 to 6 (Appendix 5.3.5.3.2.7 Table 51).

All Severe Probably or Possibly Related Unsolicited Adverse Events After MenACWY Alone, With Concomitant Vaccines, and Total MenACWY Compared With Menomune, Menactra, and Tdap Vaccines Within Each Age Group

All severe probably or possibly related AEs in each age group occurred at an incidence of less than 1% during month 1 (Appendix 5.3.5.3.2.7 Tables 50.1, 50.2, and 50.3) and months 2 to 6 (Appendix 5.3.5.3.2.7 Tables 52.1, 52.2, and 52.3). There were no clinically meaningful differences between the vaccine groups in any severe probably or possibly related AE.

2.1.2 Deaths

No deaths were reported during or after the study period in the five studies included for the proposed indication (11 to 55 year age range) (Appendix 5.3.5.3.2.7 Table 67).

Two subjects outside of the proposed indication died. Both events were assessed as unrelated to study vaccinations. Events leading to the death of these subjects are described in the following narratives.

Study V59P14: Subject (b) (6), Lung infection

- Subject (b) (6) was an 8-month-old male who died on (b) (6) (67 days after the third vaccination). Macroscopic autopsy examination suggested that the subject died of a lung infection. The subject also had traces of trauma, although not related to death. The full autopsy report, histological examination, medical records and the death certificate were not available at the time of this application.

Study V59P17: Subject (b) (6), Hypovolemic shock

- Subject (b) (6) was a 58-year-old woman vaccinated with MenACWY on (b) (6) (b) (6) The subject died on (b) (6) due to hypovolemic shock. In

(b) (6), the subject presented with kidney stones, and a "double J" stent was placed. After placement, on (b) (6), (105 days after vaccination), the subject presented to the hospital with dyspnea, cough, and fever. Chest x-ray showed pleural fluid and signs of consolidation. On (b) (6), the subject was referred to the intensive care unit. Abdominal CT showed perinephric abscess and air in the retroperitoneal space. On (b) (6), the retroperitoneal abscess was drained by puncture, and a nephrectomy was performed. The subject developed hypotension postsurgery and required blood transfusions, IV liquids, colloids, pressors, and vasoactive drugs. The subject began bleeding through her surgical incision, and despite laparotomy, progressed to hypovolemic shock and death on (b) (6). The investigator considered the event as not related to the investigational product.

2.1.3 Other Serious Adverse Events

As of 15 FEB 08, there have been 292 SAEs reported to the Novartis Vaccines Pharmacovigilance database in subjects who received any formulation of MenACWY or in subjects for whom the vaccine remains unknown due to the blind nature of the study (Appendix 5.3.5.3.2.7, Tables 94 and 68).

2.1.3.1 Serious Adverse Events in the Proposed Indication

A listing of all SAEs reported during studies V59P6, V59P11, V59P13, V59P17, and V59P18 submitted in support of the proposed indication is provided in Appendix 5.3.5.3.2.7 Table 68. Summaries of SAEs across vaccine groups and age groups, and narratives of vaccine- or study-related events for the proposed indication, are presented in following sections.

Three SAEs began within 7 days after vaccination but were not related to vaccination (intentional multiple drug overdose by **subject** (b) (6) in study V59P13; angioedema by **subject** (b) (6) in study V59P17; and pelvic inflammatory disease by **subject** (b) (6) in study V59P17; Appendix 5.3.5.3.2.7 Table 68).

One SAE from study V59P18 (**subject** (b) (6), hypophyseal adenoma) led to withdrawal of the subject from the study, but this event was not related to study vaccine. A brief narrative of this SAE is provided below.

Study V59P18: Subject (b) (6), Hypophyseal adenoma

Subject (b) (6) was a 12-year-old adolescent female who was randomized to group I. The investigational vaccine, MenACWY, and licensed Tdap, and HPV were administered on (b) (6) (day 1). In (b) (6), approximately 6 months prior to enrollment, the subject consulted a nutritionist with the complaint of weight gain despite changes in diet and exercise. She reported no significant medical history at time of enrollment (body mass index [BMI] 24.9). In (b) (6) she was referred to an endocrinologist by an

outside physician, who found a high urinary cortisol level on examination. This endocrinologist then referred her to the endocrinology service at (b) (6) (b) (6) and admitted on (b) (6) (day 17). After admission, a dexamethasone suppression test showed cortisol levels 20% higher than normal.

While the CT scan done on (b) (6) was normal, the magnetic resonance scan done on (b) (6) showed a result suggestive of hypophyseal microadenoma. The subject was discharged from the hospital on (b) (6) with a future date for surgery planned. She was rehospitalized on (b) (6) and taken to surgery on (b) (6) for removal of hypophyseal adenoma. The end date for hypophyseal microadenoma was considered to be (b) (6) and the subject was considered completely recovered. During hospitalization, the subject developed transitory Diabetes Insipidus, considered secondary to removal of the hypophysis. Diabetes Insipidus resolved on the day of discharge, (b) (6); the subject was considered completely recovered from this event. Cushing's syndrome was considered to be ongoing, because she continues to take steroid medication. The subject was discontinued from study on (b) (6) (dropout due to SAE). The events of Cushing's syndrome, hypophyseal adenoma, and postsurgical Diabetes Insipidus were considered by the investigator as not related to investigational vaccine.

Three SAEs from study V59P13 (please see CSR V59P13, section 5.3.5.1.14) had epilepsy-related diagnoses. All three subjects (subjects (b) (6) (b) (6) and (b) (6)) had received MenACWY, but each SAE was considered unrelated to vaccination, as described in the following narratives.

Study V59P13: Subject (b) (6), Simple partial seizure

- Subject (b) (6) was a 17-year-old female who received MenACWY on (b) (6) (b) (6) and was admitted on (b) (6), 25 days after vaccination, after a "seizure-like spell of staring, mouth drooping, and unresponsiveness." The subject went to the Emergency Department on the evening of (b) (6) after a prior visit to the ER on (b) (6) for a sudden onset of weakness, feeling faint, dizziness, followed by leg and arm numbness with tingling, headache, and left facial numbness. An EEG done on (b) (6) showed right temporoparietal sharp spikes indicating potential regions of cortical irritability that may be epileptogenic. MRI, ophthalmology exam, and lumbar puncture were normal, and the MRI showed a congenitally absent right A1 segment with a large anterior communicating artery and good flow through both ACAs. The subject was discharged from the hospital on (b) (6) in stable condition with discharge diagnoses of "possible simple complex partial seizure" and depression. Because the description of the seizure-like spell included no loss of consciousness, the diagnosis term was later changed to "possible simple partial seizure".

Study V59P13: Subject (b) (6), Juvenile myoclonic epilepsy

- Subject (b) (6) was a 17-year-old male (date of MenACWY vaccination (b) (6) (b) (6) who had a seizure on (b) (6) 35 days after receiving the study vaccine. The subject was transported by ambulance to the ED after the mother witnessed what appeared to be a tonic-clonic seizure lasting 3 minutes with loss of consciousness and confusion after the seizure. Prior to the seizure, he had been working at the computer on school work for 2 days with only 3 to 4 hours of sleep. A CT scan of the head was normal. During an outpatient neurology consultation on (b) (6) the neurological exam was normal. The assessment indicated a provoked single seizure with sleep deprivation in connection to a school project. The MRI done on (b) (6) showed no focal lesion to account for seizure. A note from a neurologist seen for a second opinion on (b) (6) confirmed the diagnosis of juvenile myoclonic epilepsy from his earlier visit with a neurologist.

Study V59P13: Subject (b) (6), Primary generalized idiopathic epilepsy

- Subject (b) (6) was a 40-year-old female who was vaccinated with MenACWY on (b) (6) She was admitted to the hospital for a seizure on (b) (6) 151 days after receiving the study vaccine. While on vacation in (b) (6) the subject experienced a first-time generalized epileptic seizure after 24 hours of sleep deprivation. She was admitted to the hospital on (b) (6) for evaluation. Her laboratory data, lumbar puncture, CT scan, and MRI were normal. Her EEG noted few generalized as well as focal (posterior and right temporal) spike/wave complexes. She was discharged from the hospital on (b) (6) On return from vacation, she was re-evaluated on (b) (6) A repeat EEG on (b) (6) noted no epileptiform activity but showed a definite photoconvulsive response with photic stimulation that outlasted the duration of the photic stimulation with spike wave discharges. Her results were interpreted as showing an elevated seizure disposition of unknown etiology.

As these events occurred 25 days to 151 days after vaccination and well outside of the 72-hour window after which seizures would typically be considered as associated with inactivated vaccines (Brown N et al, 2007). These events did not present evidence of an increased risk of seizure after MenACWY. In addition, in two of the cases, factors such as sleep deprivation and photic stimulation were associated with the seizure events.

Most Frequent Serious Adverse Events: Total MenACWY Compared With Menactra

Less than 1% of both total MenACWY (40 of 6185 subjects = 0.6%) and Menactra (13 of 1757 subjects = 0.7%) groups reported at least one SAE from vaccination day through the 6-month follow-up in the five studies supporting the proposed indication (Appendix

5.3.5.3.2.7 Table 69). Seven subjects reported SAEs during month 1 (Appendix 5.3.5.3.2.7 Table 71), and 31 subjects reported SAEs during months 2 to 6 (Appendix 5.3.5.3.2.7 Table 73). All of the individual SAEs occurred at an incidence of less than 1%, and there were no clinically meaningful differences in SAE incidence between total MenACWY and Menactra groups.

SAEs reported by more than one total MenACWY subject each were spontaneous abortion (4 subjects), appendicitis and road traffic accident (3 subjects each), and suicide attempt (2 subjects; Appendix 5.3.5.3.2.7 Table 69). Two Menactra subjects reported intervertebral disc protrusion; other Menactra SAEs were reported by one subject each. There were no clinically meaningful differences between the two groups in any single SAE.

All Serious Adverse Events After MenACWY and Comparators Within Each Age Group

All SAEs in each age group occurred at an incidence of less than 1% during month 1 and during months 2 through 6 (Appendix 5.3.5.3.2.7 Tables 72.1, 72.2, 72.3, 74.1, and 74.3). Twenty-two of 40 MenACWY subjects with at least one SAE were reported in the 11 to 18 year age group (most frequent, two subjects each with appendicitis and road traffic accident), 11 of 40 subjects in the 19 to 34 year group (most frequent, three subjects with spontaneous abortion), and 7 of 40 subjects in the 35 to 55 year group (one subject each with one of seven SAEs). There were no clinically meaningful differences in any SAE between the vaccine groups within age groups.

Most Frequent Probably or Possibly Related Serious Adverse Events: Total MenACWY Compared With Menactra

A single SAE was considered probably or possibly related to study vaccine (spontaneous abortion in a 19 to 34 year old MenACWY subject in the V59P17 study; Appendix 5.3.5.3.2.7 Tables 75, 76.1, 76.2, and 76.3). This event was also considered unexpected and was reported as a suspected unexpected serious adverse reactions (SUSAR).

Narrative of SUSAR Within the Age Indication

Study V59P17: Subject (b) (6), Spontaneous abortion

- Subject (b) (6) was a 34-year-old female who received one vaccination of MenACWY on (b) (6). A urine pregnancy test was negative on that day. On (b) (6) (44 days after vaccination), the subject was seen in clinic for vaginal bleeding and low abdominal pain for the previous 20 hours. At that time, her serum B-HCG of 2248 mIU/mL (consistent with a fourth or fifth week of pregnancy) and ultrasound showed neither a gestational sac nor evidence of an adnexal solid mass or cyst. Subject was discharged on the same day with a diagnosis of spontaneous abortion. On (b) (6) the serum B-HCG was found

to be 543 mIU/mL, ultrasound still showed no adnexal solid mass or cyst, and she was diagnosed with a complete spontaneous abortion. She was then considered completely recovered. Subject reported a history of a previous normal intrauterine pregnancy with a normal delivery. The investigator assessed the event as serious based on the criteria of "medically significant" and possibly related to study vaccine due to temporal association of vaccination and SAE.

An analysis of similar events showed there were three other subjects with spontaneous abortions, all in subjects that received MenACWY (subject (b) (6) in V59P13 and subjects (b) (6) and (b) (6) from study V59P17), which were all considered unrelated to vaccination (please refer to narratives for these events in the CSR V59P17, section 5.3.5.1.15 and CSR V59P13, section 5.3.5.1.14 for subject (b) (6)).

2.1.3.2 Serious Adverse Events in Completed Studies Outside of the Proposed Indication

Among all the SAEs reported, four events outside of the proposed indication have been considered unexpected and possibly related to Novartis MenACWY (i.e., SUSARs), and one event was considered expected and possibly related. The appropriate competent authorities have been notified of these events. Two SUSARs were reported in study V59P5 and two were reported in study V59P14. There was one expected, possibly related event and one study-conduct related SAE reported from study V59P10.

A brief overview of each of the cases is provided below. A more complete clinical summary can be found in the Investigator Brochure (Edition 11; Issue date 14 FEB 08) with the exception of the events from study V59P14 that occurred subsequent to this edition (see descriptions of SAEs for subjects (b) (6) and (b) (6).

Narratives of SUSARs Outside of Age Indication

Study V59P5: Subject (b) (6), Supraventricular tachycardia

- In study V59P5, supraventricular tachycardia (SVT) was reported in a child (**subject** (b) (6)) that had been diagnosed and treated for SVT since 19 days of age. This event occurred on the same day as the second vaccination of Novartis MenACWY administered concomitantly with routine vaccinations.

Study V59P5: Subject (b) (6), idiopathic thrombocytopenic purpura

- In study V59P5, idiopathic thrombocytopenic purpura (ITP) was reported in a child (**subject** (b) (6)) that had rash and thrombocytopenia following the fourth vaccination of Novartis MenACWY (with adjuvant) vaccine. Seven days after vaccination with the fourth dose of MenACWY, the subject was observed to have a rash on his lower limbs described as bruises. The following morning the rash was observed to have spread to involve a greater proportion of his lower limbs as

well as his upper limbs with sparing of his face and torso, at which point investigators were contacted for advice. The subject was admitted to the hospital: initial full blood count revealed thrombocytopenia (with a platelet count of 6 X 10^9/liter). Hemoglobin and neutrophil counts were normal, as was a preliminary blood film. A provisional diagnosis of idiopathic thrombocytopenic purpura was made.

On further review of the child's history, it was noted that he had experienced a presumed viral infection approximately 2 weeks before the booster phase of the study and 20 days before the onset of symptoms, manifesting as oral ulceration and mild rash. The subject had been treated for the infection with paracetamol and ibuprofen and recovered within a couple of days.

The investigator assessed the event as possibly related to vaccination only because of the temporal association. A follow-up on the health status of the subject and repeat laboratory exams confirmed that the child recovered completely.

Study V59P14: **Subject** (b) (6) **, Kawasaki's disease**

- In study V59P14, a 7-month-old male subject (**subject** (b) (6)) was diagnosed with Kawasaki's disease. He was hospitalized 31 days after vaccination with the study vaccine MenACWY, along with Pediarix, Prevnar, ActHib, and Rotateq with a presentation consistent with an early or incomplete Kawasaki's disease. The subject was treated with intravenous immunoglobulin (IVIG), had no evidence of cardiac abnormalities, and recovered. The investigator considered this SAE possibly related to MenACWY based on the unclear etiology of Kawasaki's disease as well as the temporal relationship. Upon external review (Dr. (b) (4), (b) (6) , the case was considered to be incomplete Kawasaki's disease.

In an analysis of similar events, it was found that in study V59P7, a 3-year-old girl experienced suspected Kawasaki's disease about 5 months after administration of MenACWY with adjuvant. She had fever, conjunctivitis, and a 2-cm right cervical lymphadenopathy but no rash and no edema in her extremities (meeting two out of five diagnostic criteria). She had a highly positive CRP and pyuria but had a normal heart ultrasound. She was diagnosed with Kawasaki's Disease (imperfect) and treated with intravenous immunoglobulin and acetylsalicylic acid, with complete recovery after about 20 days. This case was considered unrelated to vaccination because of the 5-month time period between vaccination and onset of symptoms.

Note: this SUSAR was reported after the 15 FEB 08 cutoff date and is not included in Appendix 5.3.5.3.2.7 Table 94, but is included here for completeness.

Study V59P14: Subject (b) (6) , infant botulism

- Also in study V59P14, a 2-month-old male subject (**subject** (b) (6)) developed symptoms that were initially diagnosed as meningoencephalitis 1 day after vaccination with MenACWY, along with Pediarix, Prevnar, ActHib, and Rotateq.

This was reported as possibly related to vaccination based on temporal relationship. However, Clostridium botulinum toxin A was later found in the subject's stool and the initial diagnosis was changed to infant botulism. The investigator changed his initial assessment and considered the case to be unrelated to vaccination.

In each of these SUSARs noted above, the investigators assessed the event as possibly related to vaccination primarily because of a temporal association with vaccination, without other evidence suggesting a causal relationship.

Study V59P10: **Subject** (b) (6) **, Febrile seizures**

- In study V59P10, an event classified as expected and possibly related was a case of febrile seizures that started with fever of 38.5°C 3 hours after vaccination and convulsions 7 hours after vaccination in a 5-year-old child (**subject** (b) (6)) who received MenACWY. She had a pre-existing history of episodes of febrile seizures when she was 2 and 4 years old. The investigator considered the event as related to vaccination.

Study V59P10: **Subject** (b) (6) **, Postvaccination tonic convulsions**

- In study V59P10, a 7-year-old child (**subject** (b) (6)) was diagnosed with postvaccination tonic convulsions that were considered study-conduct related. Fifteen minutes after vaccination with a still-blinded vaccine (Menomune or MenACWY), the subject had a tonic convulsion with enuresis. The episode was characterized by hypertonia and a postictal period lasting approximately 3 to 5 minutes. The subject received oxygen therapy and fully recovered. One hour later, the subject was hospitalized for observation and, without additional treatment, was discharged 15 hours later without sequelae. On review of the child's history, it was reported that the child had four similar episodes in the past: all of them were considered as "vagal crises". Three of these events occurred in close association with vaccine administration. No medical documentation or information on the name or type of vaccine administered at the time of the previous episodes was available. The duration of the SAE was 1 day, the severity was mild, and the subject recovered. The event was assessed by the investigator as not related to the vaccine itself but related to the study conduct (i.e., the "act of vaccination").

Table 2.1.3.2-1 lists SAEs outside of the proposed indication that were considered by the investigator to be probably or possibly related to study vaccine.

Table 2.1.3.2-1 Listing of Probably or Possibly Related Serious Adverse Reactions Outside of the Proposed Indication

Protocol	Subject ID	Subject Age	Condition	Onset From Last MenACWY Vaccination	Outcome	Vaccine Group (µg Ag Content)	Relationship to Study Vaccine
V59P5	(b) (6)	67 mo.	Idiopathic thrombocytopenic purpura	7 days	Complete recovery	Men ACWY (10-5-5-5 Ad+)	Possibly related
	(b) (6)	58 mo.	Supraventricular Tachycardia (SVT)	5 hr 50 min 36 days	Complete recovery	Men ACWY (10-5-5-5 Ad+)	Possibly related
V59P10	(b) (6)	5 yr.	Febrile seizure	18 hr 50 min	Complete recovery	Men ACWY Ad-/Menomune	Possibly Related
V59P14	(b) (6) [a]	7 mo	Incomplete Kawasaki's Disease	32 days	Complete recovery	Men ACWY Ad-	Possibly related

Source: Appendix 5.3.5.3.2.7 Table 94.
[a] Reported after 15 FEB 08.

2.1.4 Other Significant Adverse Events

One nonserious adverse event fromV59P13 was of interest as an immune-mediated neurologic syndrome; however, this event was considered unrelated to vaccination.

V59P13: Subject (b) (6), Myasthenia gravis

- Subject (b) (6) was enrolled at 14 years of age on (b) (6) and began treatment with Mestinon for AEs resulting in a diagnosis of myasthenia gravis on (b) (6) His symptoms began with lip and chin muscle fatigability for which he saw a physician on (b) (6) He was seen by a neurologist on (b) (6) and was diagnosed with facial weakness suggestive of facioscapulohumeral muscular dystrophy. The diagnosis of myasthenia gravis was made after his symptoms progressed and the neurologist reviewed his positive myasthenia panel. This subject's clinical syndrome began much prior to his enrollment in the study, and the investigator did not deem lip and chin muscle fatigability to qualify as a condition that would endanger the subject or affect the evaluation of safety and immunogenicity in the study. After entry, his syndrome worsened, and the investigator ultimately considered the diagnosis of myasthenia gravis to be unrelated to vaccination.

2.1.5 Analysis of Adverse Events by Organ System or Syndrome

This section evaluates the incidence of AEs grouped by MedDRA System Organ Class (SOC). Appendix 5.3.5.3.2.7 Table 93 provides the mapping of the MedDRA preferred

AE term to the corresponding SOC and lists studies and subject identification numbers associated with preferred and SOC terms.

Each of the protocols required entry of healthy subjects of various ages, and no evaluation by syndrome was possible.

2.1.5.1 All Unsolicited Adverse Events

Total MenACWY Compared With Menactra in Pooled Age Groups and Pooled Studies

Considering pooled studies and pooled age groups, 1474 (24%) total MenACWY subjects reported at least one AE in 24 MedDRA SOCs, and 443 (25%) Menactra subjects reported at least one AE in 21 SOCs (Appendix 5.3.5.3.2.7 Table 77). The most frequent SOCs for both vaccine groups were infections & infestations (7% incidence for both vaccine groups), gastrointestinal disorders (4% incidence for both), general disorders & administrative site conditions (4% for total MenACWY and 3% for Menactra), and nervous system disorders (3% for MenACWY and 5% for Menactra). Less frequent SOCs were also similar between the two groups. There were no clinically meaningful differences between total MenACWY and Menactra in the incidence of AEs categorized by SOC in the pooled studies and pooled age groups.

MenACWY Alone and Total MenACWY Compared With Other Vaccine Groups in the 11 to 18, 19 to 34, and 35 to 55 Year Age Groups

There were no differences between the total MenACWY group compared with Menactra, Menomune, and Tdap groups in incidence of AEs categorized by SOC in the 11 to 18 year, 19 to 34 year, or 35 to 55 year age groups (Appendix 5.3.5.3.2.7 Tables 78.1, 78.2, and 78.3). With minor variations, all SOCs were similar across vaccine groups in each age group.

2.1.5.2 Probably or Possibly Related Adverse Events

Total MenACWY Compared With Menactra in Pooled Age Groups and Pooled Studies

In pooled studies and pooled age groups, 365 (6%) total MenACWY subjects had AEs considered probably or possibly related to vaccines in 18 MedDRA SOCs, and 130 (7%) Menactra subjects had at least one AE in 21 SOCs (Table 2.1.5.2-1 and Appendix 5.3.5.3.2.7 Table 79). The most frequent SOCs for both vaccine groups were general disorders & administrative site conditions (3% for total MenACWY and 2% for Menactra), nervous system disorders (2% for both vaccine groups), gastrointestinal disorders (1% incidence for both), and infections & infestations (1% incidence for both vaccine groups). Less frequent SOCs were also similar between the two groups. There were no differences in incidence of probably and possibly related AEs categorized by

SOC between total MenACWY and Menactra in in the pooled studies and pooled age groups.

Table 2.1.5.2-1 Summary of Probably or Possibly Related Unsolicited Adverse Events by MedDRA System Organ Class: Total MenACWY Across Age Groups

Unsolicited Adverse Events: MedDRA System Organ Class	Total MenACWY Age Groups			Total MenACWY N=6185	Menactra N=1757
	11 – 18 N=3579	19 – 34 N=1145	35 - 55 N=1461		
Any AE	147 (4)	87 (8)	131 (9)	365 (6)	130 (7)
General disorders & administration site conditions	71 (2)	32 (3)	65 (4)	168 (3)	36 (2)
Nervous system disorders	31 (1)	33 (3)	30 (2)	94 (2)	42 (2)
Gastrointestinal disorders	27 (1)	18 (2)	9 (1)	54 (1)	21 (1)
Musculoskeletal connective tissue and bone disorders	17 (<1)	7 (1)	26 (2)	50 (1)	21 (1)
Infections & infestations	11 (<1)	10 (1)	17 (1)	38 (1)	14 (1)
Skin and subcutaneous tissue disorders	10 (<1)	6 (1)	16 (1)	32 (1)	16 (1)

Appendix 5.3.5.3.2.7 Table 79. Criterion for inclusion in this table = at least 1% incidence in the system organ class.
[a]Total exposed to final MenACWY formulation.

MenACWY Alone and Total MenACWY Compared With Other Vaccine Groups in the 11 to 18, 19 to 34, and 35 to 55 Year Age Groups

There were no differences between the total MenACWY group compared with Menactra, Menomune, and Tdap groups in probably or possibly related AEs in SOCs in the 11 to 18 year, 19 to 34 year, or 35 to 55 year age groups (Appendix 5.3.5.3.2.7 Tables 80.1, 80.2, and 80.3). All SOCs were similar across vaccine groups in each age group.

2.2 Narratives

Hyperlinks to full narratives for the following events are provided below.

- Deaths: V59P14 subject (b) (6), V59P17 subject (b) (6) (section 2.1.2);
- SAE leading to withdrawal: V59P18 subject (b) (6) (section 2.1.3.1) (also please refer to CSR V59P18, section 5.3.5.1.16);
- Seizures: V59P13 subjects (b) (6) (b) (6), and (b) (6) (section 2.1.3.1) (also please refer to CSR V59P13, section 5.3.5.1.14);
- Spontaneous abortions: V59P17 subjects (b) (6), (b) (6) (section 2.7.4.2.1.3.1) (also please refer to CSR V59P17, section 5.3.5.1.15);

- SUSARs outside of indication: V59P5 subjects (b) (6) and (b) (6) (section 2.7.4.2.1.3.2) and V59P14 subject (b) (6) ;
- Other SAEs of interest outside of indication: V59P10 subjects (b) (6) and (b) (6) (also please refer to CSR V59P10, section 5.3.5.4.13).

3 Clinical Laboratory Evaluations

Clinical laboratory tests (chemistry, hematology, and routine urinalyses) were carried out on samples provided by participants in the first two studies (V59P1 and V59P3) conducted under the clinical development plan for MenACWY. Study V59P1 collected samples before vaccination and 1 month after MenACWY with adjuvant, and study V59P3 collected samples before and 1 month after MenACWY with and without adjuvant (please see CSRs V59P1, section 5.3.5.4.1 and V59P3, section 5.3.5.4.6). No consistent or clinically significant changes in laboratory values were observed in either V59P1 or V59P3. Clinical laboratory results obtained are available within each CSR (please see CSRs V59P1 and V59P3, section 12.4). .

4 Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically significant changes in physical findings or vital signs were reported during the trials. A physical examination including vital signs (heart rates, blood pressures, oral or axillary temperature) was required for entry into any study. An integrated analysis of fever has been presented in sections 2.1.1 and 2.1.2.

5 Safety in Special Groups and Situations

5.1 Intrinsic Factors

There is no evidence available in these studies that would support evaluation of genetic or physiological factors influencing results of vaccine studies in general or the MenACWY studies in the Application in particular.

5.1.1 Summary of MenACWY Safety by Age Group

As per discussion with CBER, meningococcal vaccine trials evaluate safety for 11 to 18, 19 to 34, and 35 to 55 year age groups. These groups are described separately throughout this summary. There were only marginal differences in the safety profiles in these age groups.

5.1.1.1 Solicited Adverse Events

5.1.1.1.1 Overview of Reactogenicity by Age Group

An overview of incidence and severity of MenACWY reactogenic events in pooled studies across 11 to 18, 19 to 34, and 35 to 55 year age groups is provided in Table 5.1.1.1.1-1. Study results are provided in individual CSRs (section 5.3.5.1).

In total MenACWY, the percentages of subjects with any reaction, any local reaction, and any systemic reaction were higher in the 11 to 18 year and 19 to 34 year age groups (67% and 65%, respectively) than in the 35 to 55 year age group (56%; Table 5.1.1.1.1-1). The incidence of any severe reaction was similar among the age groups (range, 7% to 9%). The 35 to 55 year age group reported fewer instances of both local and systemic reactions (41% and 36%, respectively) than the 11 to 18 year (49% and 49%) and 19 to 34 year (52% and 40%) age groups. No differences among the age groups were noted in other reactions or in reactions that were severe in intensity.

In conclusion, the incidence of any injection site reactions, local reactions, and systemic reactions to total MenACWY was higher in 11 to 18 year and 19 to 34 year age groups. However, the incidence of severe reactions was generally comparable among the age groups.

Table 5.1.1.1.1-1 Overview of Reactogenicity: Total MenACWY Across Age Groups

Solicited Reaction	Category	Total MenACWY[a] Age Group			Total MenACWY N=6185	Menactra N=1757
		11 – 18 N=3579	19 – 34 N=1145	35 - 55 N=1461		
Any reaction	Any	2406 (67)	743 (65)	817 (56)	3966 (64)	1146 (65)
	Severe	320 (9)	87 (8)	100 (7)	507 (8)	110 (6)
Local	Any	1739 (49)	590 (52)	605 (41)	2934 (47)	906 (52)
	Severe [b]	132 (4)	40 (3)	53 (4)	225 (4)	54 (3)
Systemic	Any	1748 (49)	460 (40)	532 (36)	2740 (44)	725 (41)
	Severe [b]	233 (7)	56 (5)	66 (5)	355 (6)	70 (4)
Other	Any	657 (18)	225 (20)	298 (20)	1180 (19)	345 (20)

Appendix 5.3.5.3.2.7 Tables 6 and 10. Subjects with at least one local and/or systemic reaction. Cell entries are n (%).
Any severe = severe local reactions or severe systemic reactions. [a] Total number exposed to MenACWY either alone or with concomitant vaccines. [b] Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥39.0°C.

5.1.1.1.2 Summary of Individual Signs of Reactogenicity by Age Group

The MenACWY incidence of individual local and systemic reactions was generally comparable between age groups; however, the 35 to 55 year age group reported 10% lower incidence of injection site pain than the 19 to 34 year group (Table 5.1.1.1.2-1), 10% lower incidence of myalgia than the 11 to 18 year group, and 9% lower incidence of headache than the 11 to 18 year group. Severe individual signs of local and systemic reactogenicity were of low incidence and were comparable among the age groups.

Table 5.1.1.1.2-1 Summary of Individual Signs of Reactogenicity: Total MenACWY Across Age Groups: Days 1 to 7

Solicited Reaction	Category	Total MenACWY Age Group			Total MenACWY N=6185	Menactra N=1757
		11 – 18 N=3579	19 – 34 N=1145	35 - 55 N=1461		
LOCAL REACTIONS						
Pain	Any	1501 (42)	510 (45)	513 (35)	2524 (41)	816 (46)
	Severe	56 (2)	19 (2)	25 (2)	100 (2)	36 (2)
Erythema	Any	552 (15)	192 (17)	182 (12)	926 (15)	231 (13)
	>50 mm	52 (1)	20 (2)	25 (2)	97 (2)	17 (1)
Induration	Any	468 (13)	150 (13)	157 (11)	775 (13)	203 (12)
	>50 mm	59 (2)	14 (1)	13 (1)	86 (1)	15 (1)
SYSTEMIC REACTIONS						
Chills	Any	380 (11)	79 (7)	86 (6)	545 (9)	120 (7)
	Severe	33 (1)	11 (1)	9 (1)	53 (1)	6 (<1)
Nausea	Any	440 (12)	97 (8)	88 (6)	625 (10)	142 (8)
	Severe	33 (1)	8 (1)	6 (<1)	47 (1)	9 (1)
Malaise	Any	550 (15)	205 (18)	206 (14)	961 (16)	285 (16)
	Severe	55 2)	30 (3)	22 (2)	107 (2)	22 (1)
Myalgia	Any	791 (22)	160 (14)	179 (12)	1130 (18)	280 (16)
	Severe	74 (2)	16 (1)	14 (1)	104 (2)	17 (1)
Arthralgia	Any	402 (11)	74 (6)	104 (7)	580 (9)	130 (7)
	Severe	41 (1)	6 (1)	14 (1)	61 (1)	10 (1)
Headache	Any	1207 (34)	316 (28)	358 (25)	1881 (30)	491 (28)
	Severe	138 (4)	27 (2)	38 (3)	203 (3)	38 (2)
Rash	Any	82 (3)	39 (3)	39 (3)	160 (3)	42 (2)
Fever	38°C - 38.9°C	77 (2)	21 (2)	27 (2)	125 (2)	27 (2)
	39°C - 39.9°C	17 (<1)	8 (1)	5 (<1)	30 (<1)	8 (<1)
	≥ 40°C	2 (<1)	2 (<1)	2 (<1)	6 (<1)	2 (<1)
OTHER REACTIONS						
Stayed home	Yes	176 (5)	47 (4)	45 (3)	268 (4)	63 (4)
Analgesic/ antipyretic	Yes	576 (16)	208 (18)	282 (19)	1066 (17)	326 (19)

Appendix 5.3.5.3.2.7 Table 14. Cell entries are n (%).

Local reactions were more frequently reported in days 1 to 3 after vaccination in each of the three age groups (Appendix 5.3.5.3.2.7 Table 18) than during days 4 to 7 (Appendix 5.3.5.3.2.7 Table 22). Systemic reactions were generally reported with similar incidence in the three age groups in both time periods after vaccination. The incidence of severe

individual local and systemic reactions was comparable among the three age groups and between the two postvaccination time periods.

Appendix 5.3.5.3.2.7 Table 26 summarizes the time of first onset of local, systemic, and other reactions within the first 7 days after vaccination. Both local and systemic reactions frequently began early in the 7-day postvaccination interval and did not differ among the age groups.

5.1.1.2 Unsolicited Adverse Events

5.1.1.2.1 Overview of Unsolicited Adverse Events by Age Group

During the first month after vaccination, 1076 total MenACWY subjects (17%) reported at least one AE, and the incidence of unsolicited adverse events was similar among the three age groups (range, 16% to 20%; Table 5.1.1.2.1-1).

During month 1, 59 subjects (1%) reported at least one severe AE, and the incidence of severe AEs was 1% in each age group (Table 5.1.1.2.1-1). Probably or possibly related AEs were reported by 4% of subjects in the 11 to 18 year group and by 8% to 9% of subjects in the 19 to 34 year and 35 to 55 year groups, respectively. Probably or possibly related AEs that were severe in intensity were reported by no greater than 1% of subjects in each age group. No deaths were reported during the month following vaccination. During month 1, seven subjects reported SAEs. The percentages of subjects reporting any SAE or any probably or possibly related SAE were no greater than 1% in each age group.

During months 2 to 6, 460 (9%) of total MenACWY subjects reported at least one AE; the incidence of AEs was 11%, 7%, and 8% in the 11 to 18 year, 19 to 34 year, and 35 to 55 year subjects, respectively (Table 5.1.1.2.1-1). Thirty-one total MenACWY subjects reported at least one SAE; however a single subject experienced at least one SAE that was probably or possibly related to study vaccine. No deaths were reported during the second through sixth months following vaccinations.

Table 5.1.1.2.1-1 Overview of Unsolicited Adverse Events: Comparing Total ACWY Across Age Groups

Time	Overview of Unsolicited Adverse Events (AE)	Total MenACWY Age Group			Total MenACWY	Menactra
		11 – 18	19 – 34	35 - 55		
Month 1	**Total exposed: N**	**3579** [a]	**1145**	**1461**	**6185** [a]	**1757**
	Any AE	586 (16)	205 (18)	285 (20)	1076 (17)	356 (20)
	Any severe AE	29 (1)	12 (1)	18 (1)	59 (1)	16 (1)
	Possibly/probably related AE	141 (4)	86 (8)	130 (9)	357 (6)	128 (7)
	Severe possibly/probably related AE	7 (<1)	5 (<1)	9 (1)	21 (<1)	5 (<1)
	Any SAE	6 (<1)	1 (<1)	0	7 (<1)	4 (<1)
	Possibly/probably related SAE	0	0	0	0	0
	Death	0	0	0	0	0
Months 2 to 6	**Total exposed: N**	**2479** [a]	**1132**	**1457**	**5068** [a]	**1746**
	Any AE	269 (11)	76 (7)	115 (8)	460 (9)	134 (8)
	Any severe AE	23 (1)	9 (1)	10 (1)	42 (1)	14 (1)
	Possibly/probably related AE	0	2 (<1)	1 (<1)	3 (<1)	1 (<1)
	Severe possibly/probably related AE	0	0	0	0	0
	Any SAE	14 (1)	10 (1)	7 (<1)	31 (1)	10 (1)
	Possibly/probably related SAE	0	1 (<1)	0	1 (<1)	0
	Death	0	0	0	0	0

Source: month 1: Appendix 5.3.5.3.2.7 Tables 32, 37, 43, 49, 67, and 73; months 2 to 6: 35, 39, 47, 51, 71, 75.
Total exposed = number of subjects with at least one event during the time period indicated. Cell entries are N or n (%).
[a] Study V59P18 is ongoing; only safety data for month 1 is included for these subjects.

5.1.1.2.2 Summary of Most Frequent Treatment Emergent Adverse Events by Age Group and for Total MenACWY

No clinically meaningful differences among the three age groups were seen in all unsolicited AEs during month 1 or months 2 to 6.

During month 1 after the vaccination, headache was the most frequently reported AE in the total MenACWY group (Table 5.1.1.2.2-1 and Appendix 5.3.5.3.2.7 Table 32). The

incidence of headache during month 1 was similar among the three age groups (range, 2% to 3%). All other AEs occurred with an incidence of 1% or less. Among AEs that were considered probably or possibly related to study vaccines, headache and malaise, injection site erythema, injection site pain, and injection site pruritis (all 1%) were most frequently reported by total MenACWY subjects (Appendix 5.3.5.3.2.7 Table 43). All related severe AEs were reported by less than 1% of subjects among the age groups (Appendix 5.3.5.3.2.7 Table 49).

During months 2 to 6, all of the AEs were reported by less than 1% of the subjects (Appendix 5.3.5.3.2.7 Table 35). The most frequently reported AEs during months 2 to 6 were pharyngitis, influenza, bronchitis, headache, and pneumonia (all less than 1% incidence); no differences were noted between age groups. Single reports of malaise, synovial cyst, headache, and spontaneous abortion were considered probably or possibly related to study vaccines (Appendix 5.3.5.3.2.7 Table 47). There were no related severe AEs (Appendix 5.3.5.3.2.7 Table 51).

Table 5.1.1.2.2-1 Summary of Unsolicited Adverse Events Within 1 Month After Vaccination: Total MenACWY Across Age Groups and Sorted by Descending Frequency

Unsolicited Adverse Events: MedDRA Preferred Term	Total MenACWY Age Group			Total MenACWY N=6185	Menactra N=1757
	11 – 18 N=3579	19 – 34 N=1145	35 – 55 N=1461		
Any AE	**586 (16)**	**205 (18)**	**285 (20)**	**1076 (17)**	**356 (20)**
Headache	58 (2)	29 (3)	31 (2)	118 (2)	37 (2)
Malaise	24 (1)	16 (1)	18 (1)	58 (1)	10 (1)
Pharyngolaryngeal pain	32 (1)	7 (1)	12 (1)	51 (1)	15 (1)
Dysmenorrhoea	30 (1)	13 (1)	6 (<1)	49 (1)	5 (<1)
Nasopharyngitis	17 (<1)	17 (1)	13 (1)	47 (1)	15 (1)
Nausea	25 (1)	12 (1)	3 (<1)	40 (1)	7 (<1)
Diarrhoea	16 (<1)	12 (1)	9 (1)	37 (1)	17 (1)
Upper respiratory tract infection	29 (1)	4 (<1)	3 (<1)	36 (1)	12 (1)
Arthralgia	14 (<1)	7 (1)	15 (1)	36 (1)	16 (1)
Myalgia	11 (<1)	8 (1)	17 (1)	36 (1)	12 (1)
Cough	26 (1)	3 (<1)	4 (<1)	33 (1)	4 (<1)
Injection site erythema	11 (<1)	12 (1)	9 (1)	32 (1)	2 (<1)
Pharyngitis	20 (1)	3 (<1)	7 (<1)	30 (<1)	5 (<1)
Back pain	7 (<1)	6 (1)	16 (1)	29 (<1)	10 (1)
Injection site pain	6 (<1)	9 (1)	13 (1)	28 (<1)	8 (<1)
Injection site pruritis	11 (<1)	4 (<1)	12 (1)	27 (<1)	5 (<1)
Vomiting	18 (1)	1 (<1)	5 (<1)	24 (<1)	9 (1)
Abdominal pain upper	16 (<1)	6 (1)	2 (<1)	24 (<1)	3 (<1)
Abdominal pain	11 (<1)	6 (1)	4 (<1)	21 (<1)	12 (1)
Injection site induration	9 (<1)	6 (1)	6 (<1)	21 (<1)	1 (<1)
Dizziness	7 (<1)	8 (1)	6 (<1)	21 (<1)	16 (1)
Pain in extremity	9 (<1)	2 (<1)	9 (1)	20 (<1)	15 (1)
Pyrexia	17 (<1)	1 (<1)	2 (<1)	20 (<1)	0
Sinusitis	13 (<1)	4 (<1)	3 (<1)	20 (<1)	6 (<1)

Appendix 5.3.5.3.2.7 Table 32. Criteria for inclusion in this table = 20 subjects with the AE in the total MenACWY group. Cell entries are N or n (%).
[a]Total exposed to final MenACWY formulation

The incidence of all unsolicited AEs was similar among the different MedDRA system organ classes (Table 5.1.1.2.2-2).

Table 5.1.1.2.2-2 Summary of Unsolicited Adverse Events by MedDRA System Organ Class: Total MenACWY Across Age Groups Compared With Menactra in Pooled Age Groups and Pooled Studies

Unsolicited Adverse Events: MedDRA System Organ Class	11 – 18 N=3579	19 – 34 N=1145	35 - 55 N=1461	Total MenACWY N=6185	Menactra N=1757
Any AE	**846 (24)**	**259 (23)**	**369 (25)**	**1474 (24)**	**443 (25)**
Infections & infestations	263 (7)	80 (7)	99 (7)	442 (7)	121 (7)
General disorders & administration site conditions	123 (3)	49 (4)	81 (6)	253 (4)	54 (3)
Gastrointestinal disorders	130 (4)	58 (5)	49 (3)	237 (4)	73 (4)
Nervous system disorders	107 (3)	53 (5)	56 (4)	216 (3)	84 (5)
Musculoskeletal, connective tissue & bone disorders	73 (2)	27 (2)	76 (5)	176 (3)	81 (5)
Respiratory, thoracic & mediastinal disorders	113 (3)	22 (2)	36 (2)	171 (3)	38 (2)
Injury & poisoning	122 (3)	17 (1)	21 (1)	160 (3)	56 (3)
Skin & subcutanous tissue disorders	60 (2)	11 (1)	22 (2)	93 (2)	37 (2)
Reproductive system & breast disorders	52 (1)	16 (1)	11 (1)	79 (1)	16 (1)
Psychiatric disorders	28 (1)	8 (1)	14 (1)	50 (1)	16 (1)

Appendix 5.3.5.3.2.7 Table 77. Criterion for inclusion in this table = at least 1% incidence in the SOC..

5.1.2 Other Factors: Summary of MenACWY Reactogenicity by Gender

The five studies (V59P6, V59P11, V59P13, V59P17, and V59P18)) were pooled to provide an overall profile of MenACWY safety versus the main comparator vaccine, Menactra, as described in section 3.1.2. Within each study, the male:female ratio was well balanced between MenACWY and its comparators. However, in the pooling for the integrated analysis of safety, an imbalance in the male:female ratio was noted. Upon further evaluation, this imbalance was considered to be due at least in part to the varying study designs and study locations. Pooling the adolescent studies was problematic, because the four studies in adolescents had very different objectives, designs, and geographic locations. For this reason, further analyses were undertaken to more fully

explore the effect of male vs female (gender) differences using within-study comparisons and, to the extent possible, across-study comparisons. The effect of gender on the rate of the more infrequent unsolicited AEs was not examined due to the sparseness of the AE data.

5.1.2.1 Overview of Reactogenicity by Gender

Pooled across age groups and studies, 11% more female MenACWY subjects reported at least one local, systemic, or other reaction than male subjects (female, 69%; male, 58%: Table 5.1.2.1-1 below). The difference in incidence of any reaction was similar in local (10% difference; female, 52%; male 42%), systemic (11% difference; female, 49%; male 38%), and other reactions (difference 7%: female, 22%; male 15%). The same higher reporting pattern by females was also observed for Menactra subjects.

The incidence of severe MenACWY reactions in female subjects was 2%, 1%, and 2% greater (any, local, and systemic, respectivly) than the incidence of severe MenACWY reactions in male subjects (Table 5.1.2.1-1).

Table 5.1.2.1-1 Overview of Reactogenicity by Gender: Total MenACWY Compared With Menactra: Pooled Age Groups and Pooled Studies

Solicited Reaction	Category n (%)	Females		Males	
		Total ACWY N=3645	Menactra N=1113	Total ACWY N=2540	Menactra N=644
Any reaction	Any	2504 (69)	766 (69)	1462 (58)	380 (59)
	Severe [a]	337 (9)	92 (8)	170 (7)	18 (3)
Local	Any	1879 (52)	609 (55)	1055 (42)	297 (46)
	Severe [b]	156 (4)	45 (4)	69 (3)	9 (1)
Systemic	Any	1778 (49)	510 (46)	962 (38)	215 (33)
	Severe [b]	237 (7)	57 (5)	118 (5)	13 (2)
Other	Any	805 (22)	253 (23)	375 (15)	92 (14)

Appendix 5.3.5.3.2.7 Tables 81 and 85
Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.
[a] Most severe across all events. Any severe = severe local reactions or severe systemic reactions.
[b] Severe local reactions = severe pain or erythema/induration >50 mm; severe fever = ≥39°C.

Similar to the pooled analysis in the 11 to 18 year age group (Appendix 5.3.5.3.2.7 Table 82), more female subjects reported at least one local reactogenic event than male subjects in each study, a difference that was seen between both vaccine groups within each study.

Female vs male comparisons for MenACWY given with concomitant vaccines and for MenACWY given sequentially after Tdap and HPV are summarized in Appendix 5.3.5.3.2.7 Table 83 and 84, respectively. Severe reactions are summarized in Appendix 5.3.5.3.2.7 Tables 85, 86, 87, and 88.

5.1.2.2 Summary of Individual Signs of Reactogenicity by Gender

MenACWY female vs male differences in local reactions were due primarily to injection site pain (46% vs 34%, respectively, in Table 5.1.2-2) and induration (14% vs 11%). The incidence of erythema was the same (15%) for female and male subjects. The same pattern was observed for Menactra.

MenACWY female vs male differences in systemic reactions were due primarily to more female reporting of headache (11% difference; female, 35%; male 24%) and myalgia (4% difference; 20% vs 16%, respectively), malaise (4% difference; 17% vs 13%), and nausea (4% difference; 12% vs 8%; Table 5.1.2-2). Again, the pattern was also observed for Menactra.

In other reactions, more female than male MenACWY subjects stayed at home (7% difference; 20% vs 13%); there was no noteworthy difference in analgesic/antipyretic use (Table 5.1.2-2).

There were no consistent differences between female and male MenACWY subjects in the incidence of severe local or systemic reactions (Table 5.1.2-2). The largest female vs male difference was 2% in the incidence of headache (female 4%; male 2%). The female vs male difference was 1% or less for all other severe local and systemic reactions.

In conclusion, proportionally more females than males reported more injection site pain, headache, myalgia, staying at home, malaise, induration, and nausea. Because these findings were observed equally in each vaccine group, this suggests that female and male subjects had different reporting patterns for reactogenic events during the studies.

Table 5.1.2-2 Summary of Individual Signs of Reactogenicity by Gender: Total MenACWY Compared With Menactra: Pooled Age Groups and Pooled Studies

Solicited Reaction	Occurrence n (%)	Females		Males	
		Total ACWY N=3645	Menactra N=1113	Total ACWY N=2540	Menactra N=644
LOCAL REACTIONS					
Pain	Any	1672 (46)	554 (50)	852 (34)	262 (41)
	Severe	75 (2)	31 (3)	25 (1)	5 (1)
Erythema (mm)	Any	558 (15)	142 (13)	368 (15)	89 (14)
	> 50 mm	66 (2)	13 (1)	31 (1)	4 (1)
Induration (mm)	Any	497 (14)	144 (13)	278 (11)	59 (9)
	> 50 mm	58 (2)	13 (1)	28 (1)	2 (<1)
SYSTEMIC REACTIONS					
Chills	Any	378 (10)	93 (8)	167 (7)	27 (4)
	Severe	38 (1)	4 (<1)	15 (1)	2 (<1)
Nausea	Any	421 (12)	106 (10)	204 (8)	36 (6)
	Severe	29 (1)	7 (1)	18 (1)	2 (<1)
Malaise	Any	632 (17)	204 (18)	329 (13)	81 (13)
	Severe	72 (2)	18 (2)	35 (1)	4 (1)
Myalgia	Any	716 (20)	200 (18)	414 (16)	80 (12)
	Severe	71 (2)	14 (1)	33 (1)	3 (<1)
Arthralgia	Any	379 (10)	94 (8)	201 (8)	36 (6)
	Severe	41 (1)	8 (1)	20 (1)	2 (<1)
Headache	Any	1263 (35)	363 (33)	618 (24)	128 (20)
	Severe	146 (4)	29 (3)	57 (2)	9 (1)
Rash	Any	122 (4)	28 (3)	38 (2)	14 (2)
Fever	38°C - 38.9°C	70 (2)	18 (2)	55 (2)	9 (1)
	39°C - 39.9°C	15 (<1)	7 (1)	15 (1)	1 (<1)
	≥ 40°C	6 (<1)	2 (<1)	0	0

Solicited Reaction	Occurrence n (%)	Females		Males	
		Total ACWY N=3645	Menactra N=1113	Total ACWY N=2540	Menactra N=644
OTHER REACTIONS					
Stayed home	Yes	735 (20)	242 (22)	331 (13)	84 (13)
Analgesic/ antipyretic	Yes	169 (5)	45 (4)	99 (4)	18 (3)

Appendix 5.3.5.3.2.7 Table 89
Cell entries are number (percent) of subjects exposed with at least one local, systemic, or other reaction.

5.2 Extrinsic Factors

5.2.1 Summary of the Effect of Geographic Regions on MenACWY Safety: Demographic and Baseline Characteristics

Section 5.2.1 evaluates the effect of regional differences in subjects 19 to 55 years of age on the safety profile of MenACWY alone in comparison to Menactra alone. This section establishes the similarities in safety profile which justifies the pooling of V59P13 and V59P17 adult populations. The US study V59P13 and the Latin American study V59P17 provide the data for these comparisons.

On the average, US subjects were approximately 4 years older than Latin American subjects (Table 5.2.1-1), and the ratio of male to female subjects was about 7% to 8% less. US subjects were predominantly Caucasian (range, 78% to 81%), while Latin American subjects were predominantly Hispanic (range, 73% to 76%). US subjects were heavier by approximately12 to 13 kilograms and were 4 to 5 centimeters taller.

Table 5.2.1-1 Demographic and Baseline Characteristics: MenACWY Alone Compared With Menactra Alone Across Geographic Regions: United States Versus Latin America, Ages 19 to 55

Parameter or Characteristic	United States V59P13		Latin America V59P17	
	MenACWY Alone	Menactra	MenACWY Alone	Menactra
Total randomized: N	1023	336	1606	899
Total exposed: N	1018	336	1600	889
Safety population: N	1018	336	1588	882
Age yr mean (SD)	38.9 (9.6)	38.7 (9.9)	34.6 (10.1)	34.8 (10.4)
Male : female % : %	24 : 76	25 : 75	32 : 68	31 : 69
Race n (%):				
Asian	37 (4)	8 (2)	1 (<1)	1 (<1)
Black	85 (8)	34 (10)	132 (8)	107 (12)
Caucasian	823 (81)	261 (78)	248 (16)	127 (14)
Hispanic	60 (6)	29 (9)	1203 (76)	644 (73)
Other	13 (1)	4 (1)	4 (<1)	3 (<1)
Weight kg mean (SD)	79.06 (19.31)	80.78 (19.68)	67.32 (13.81)	67.16 (14.15)
Height cm mean (SD)	167.76 (9.58)	167.12 (8.89)	163.29 (9.70)	162.53 (9.80)

Appendix 5.3.5.3.2.7 Table 53. Please see CSR **V59P13,** section 5.3.5.1.14, Table 14.1.1.3.3; **V59P17,** section 5.3.5.1.15, Table 14.1.1.3.5.
Note: Only MenACWY alone and Menactra alone were given in these studies.

5.2.2 Summary of the Effect of Geographic Regions on MenACWY Safety: Individual Signs of Reactogenicity

Among injection site reactions (Table 5.2.2-1), the incidence of pain, erythema, and induration was similar between regions. Severe local reactions were infrequently reported (range 0% to 3%) and were also similar in incidence between regions.

Among systemic reactions (Table 5.2.2-1), the greatest regional differences in incidence of reactions was in malaise (US MenACWY, 10%; Latin America, 19%) and, to a lesser extent, chills (4% and 8%, respectively). The incidence of all other systemic reactions was similar between the regions as was the incidence of severe systemic reactions.

Latin American subjects tended to stay home more often but resort to analgesic/ antipyretic medication less often than their US counterparts (Table 5.2.2-1).

Table 5.2.2-1 Summary of Individual Signs of Reactogenicity: MenACWY Alone Versus Menactra Across Geographic Regions: United States Versus Latin America, Ages 19 to 55

Solicited Reaction	Category	United States V59P13		Latin America V59P17	
		ACWY Alone N=1018	Menactra N=336	ACWY Alone N=1588	Menactra N=882
LOCAL REACTIONS					
Pain	Any	391 (38)	137 (41)	632 (40)	392 (44)
	Severe	3 (<1)	0	41 (3)	29 (3)
Erythema	Any	167 (16)	41 (12)	207 (13)	105 (12)
	>50 mm	28 (3)	3 (1)	17 (1)	7 (1)
Induration	Any	128 (13)	29 (9)	179 (11)	115 (13)
	>50 mm	14 (1)	1 (<1)	13 (1)	10 (1)
SYSTEMIC REACTIONS					
Chills	Any	41 (4)	12 (4)	124 (8)	70 (8)
	Severe	1 (<1)	0	19 (1)	5 (1)
Nausea	Any	73 (7)	18 (5)	112 (7)	77 (9)
	Severe	4 (<1)	1 (<1)	10 (1)	4 (<1)
Malaise	Any	102 (10)	34 (10)	309 (19)	186 (21)
	Severe	9 (1)	5 (1)	43 (3)	12 (1)
Myalgia	Any	142 (14)	50 (15)	197 (12)	131 (15)
	Severe	5 (<1)	5 (1)	25 (2)	10 (1)
Arthralgia	Any	60 (6)	20 (6)	118 (7)	76 (9)
	Severe	4 (<1)	3 (1)	16 (1)	7 (1)
Headache	Any	253 (25)	84 (25)	421 (27)	254 (29)
	Severe	16 (2)	5 (1)	49 (3)	26 (3)
Rash	Any	25 (2)	2 (1)	53 (3)	22 (2)
Fever	38°C - 38.9°C	6 (1)	1 (<1)	42 (3)	22 (2)
	39°C - 39.9°C	3 (<1)	1 (<1)	10 (1)	7 (1)
	≥ 40°C	0	0	4 (<1)	2 (<1)

Solicited Reaction	Category	United States V59P13		Latin America V59P17	
		ACWY Alone N=1018	Menactra N=336	ACWY Alone N=1588	Menactra N=882
OTHER REACTIONS					
Stayed home	Yes	17 (2)	3 (1)	75 (5)	46 (5)
Analgesic/ antipyretic	Yes	240 (24)	74 (22)	250 (16)	148 (17)

Appendix 5.3.5.3.2.7 Table 54 and individual CSRs **V59P13**, section 5.3.5.1.14, Table 14.3.1.1.3.1; **V59P17**, section 5.3.5.1.15, Table 14.3.1.1.3.1. Cell entries are n (%).

5.2.3 Overview of the Effect of Geographic Regions on MenACWY Safety: Unsolicited Adverse Events

During the first month after MenACWY vaccination, the percentages of subjects who reported at least one unsolicited AE were similar between the US and Latin America (18% and 19%, respectively; Table 5.2.3-1). The incidence of any AE after Menactra vaccine was slightly less in the US than that noted after Menactra in Latin America (18% and 21%, respectively). Percentages of subjects with at least on probably or possibly related AE were also lower in the US than in Latin America after MenACWY vaccine (7% and 9%, respectively) and after Menactra (5% and 9%). More subjects reported at least one SAE during months 2 to 6 than during month 1, but there were no clinically meaningful differences between regions in SAE incidence or in any other category of unsolicited AE at any time.

Table 5.2.3-1 Overview of Unsolicited Adverse Events: MenACWY Alone Versus Menactra Across Geographic Regions: United States Versus Latin America, Ages 19 to 55

Time	Unsolicited Adverse Events	United States V59P13		Latin America V59P17	
		MenACWY Alone	Menactra	MenACWY Alone	Menactra
Month 1	**Total exposed: N**	**1018**	**336**	**1588**	**882**
	Any AE	184 (18)	60 (18)	306 (19)	187 (21)
	Any severe AE	19 (2)	4 (1)	11 (1)	7 (1)
	Possibly/probably related AE	71 (7)	17 (5)	145 (9)	78 (9)
	Severe possibly/probably related AE	8 (1)	0	6 (<1)	4 (<1)
	Any SAE	0	2 (<1)	1 (<1)	2 (< 1)
	Possibly/probably related SAE	0	0	0	0
	Death	0	0	0	0
Months 2 to 6	**Total exposed: N**	**1010**	**334**	**1579**	**882**
	Any AE	86 (9)	13 (4)	105 (7)	74 (8)
	Any severe AE	10 (1)	2 (1)	9 (1)	7 (1)
	Possibly/probably related AE	0	0	3 (<1)	1 (<1)
	Severe possibly/probably related AE	0	0	0	0
	Any SAE	7 (1)	1 (<1)	10 (<1)	7 (1)
	Possibly/probably related SAE	0	0	1 (<1)	0
	Death	0	0	0	0

Source: Appendix 5.3.5.3.2.7 Tables 57, 58, 59, 60, 61, 62, 63, 64, 67, and 68. Cell entries are N or n (%).

5.2.4 Summary of the Effect of Geographic Regions on MenACWY Safety: Unsolicited Adverse Events

The incidence of at least one headache was slightly less in the US than in Latin America for MenACWY within the first month after vaccination (2% and 3%, respectively) and Menactra (1% and 3%; Table 5.2.4-1). There were no other clinically meaningful differences between regions or between MenACWY and Menactra in any individual unsolicited AE. The most frequent AEs were headache, malaise, nasopharyngitis, and

pharynlaryngeal pain (reported at an incidence of 2% to 3% in MenACWY subjects). All other unsolicited AEs were reported by no more than 1% of the subjects in each region.

There were no AEs of at least 1% incidence reported during month 2 to month 6 (Appendix 5.3.5.3.2.7 Table 56).

Complete lists of all unsolicited AEs reported during month 1 are summarized by MedDRA system organ class in Appendix 5.3.5.3.2.7 Table 57, 58, 59, and 60. Month 2 to month 6 AEs are summarized in Appendix 5.3.5.3.2.7 Tables 61, 62, 63, and 64. Summaries by system organ class alone are provided in Table 5.2.5-1 and Appendix 5.3.5.3.2.7 Table 65.

Table 5.2.4-1 Summary of Unsolicited Adverse Events: MenACWY Alone Versus Menactra Across Geographic Regions During Month 1 by Descending Frequency: United States Versus Latin America, Ages 19 to 55

Unsolicited Adverse Evnet: MedDRA Preferred Term	United States V59P13		Latin America V59P17	
	MenACWY Alone N=1018	Menactra N=336	MenACWY Alone N=1588	Menactra N=882
Headache	16 (2)	4 (1)	44 (3)	24 (3)
Malaise	8 (1)	0	26 (2)	7 (1)
Nasopharyngitis	4 (<1)	0	26 (2)	12 (1)
Injection site pain	3 (<1)	1 (<1)	19 (1)	5 (1)
Myalgia	8 (1)	2 (1)	17 (1)	8 (1)
Pharyngolaryngeal pain	16 (2)	5 (1)	3 (<1)	2 (<1)
Arthralgia	8 (1)	0	14 (1)	13 (1)
Injection site erythema	13 (1)	1 (<1)	8 (1)	0
Back pain	10 (1)	1 (<1)	12 (1)	9 (1)
Injection site pruritus	11 (1)	1 (<1)	5 (<1)	3 (<1)
Dizziness	4 (<1)	2 (1)	10 (1)	11 (1)
Abdominal pain	1 (<1)	1 (<1)	9 (1)	10 (1)
Pain in extremity	7 (1)	1 (<1)	4 (<1)	10 (1)
Sinusitis	5 (<1)	4 (1)	2 (<1)	1 (<1)

Source: Appendix 5.3.5.3.2.7 Table 55.
Adverse events sorted by overall MenACWY frequency and occurring in at least 1% of subjects during day 1 to day 29 (month 1). No AEs meeting this criterion were reported from day 30 to study termination in these studies (Appendix 5.3.5.3.2.7 Table 56).

5.2.5 Summary of the Effect of Geographic Regions on MenACWY Safety: Unsolicited Adverse Events by MedDRA System Organ Class: All Events and All Probably or Possibly Related Events

The incidence of all unsolicited AEs mapped to MedDRA System Organ Class was similar between regions for each SOC (Table 5.2.5-1).

Unsolicited AEs considered probably or possibly related to study vaccines were also similar between the regions (Table 5.2.5-2).

Table 5.2.5-1 Summary of All Unsolicited Adverse Events by MedDRA System Organ Class: MenACWY Alone Versus Menactra Alone Across Geographic Regions: United States Versus Latin America, Ages 19 to 55

Unsolicited Adverse Events: MedDRA System Organ Class (SOC)	United States V59P13		Latin America V59P17	
	MenACWY Alone N=1018	Menactra N=336	MenACWY Alone N=1588	Menactra N=882
Any Adverse Event	246 (24)	67 (20)	382 (24)	235 (27)
Infections & infestations	58 (6)	18 (5)	121 (8)	71 (8)
General disorders & administration site conditions	49 (5)	9 (3)	81 (5)	30 (3)
Nervous system disorders	36 (4)	12 (4)	73 (5)	52 (6)
Gastrointestinal disorders	35 (3)	12 (4)	72 (5)	43 (5)
Musculoskeletal, connective tissue & bone disorders	48 (5)	11 (3)	55 (3)	51 (6)
Respiratory, thoracic & mediastinal disorders	37 (4)	7 (2)	21 (1)	12 (1)
Injury & poisoning	16 (2)	6 (2)	22 (1)	16 (2)
Skin & subcutaneous tissue disorders	10 (1)	4 (1)	23 (1)	18 (2)
Reproductive system & breast disorders	10 (1)	5 (1)	17 (1)	9 (1)
Psychiatric disorders	18 (2)	3 (1)	4 (<1)	4 (<1)
Blood & lymphatic system disorders	4 (<1)	1 (<1)	11(1)	4 (<1)
Vascular disorders	8 (1)	3 (1)	6 (<1)	7 (1)
Eye disorders	5 (<1)	0	5 (<1)	5 (1)
Ear & labyrinth disorders	2 (<1)	1 (<1)	7 (<1)	7 (1)
Renal & urinary disorders	4 (<1)	2 (1)	1 (<1)	1 (<1)
Immune system disorders	3 (<1)	2 (1)	1 (<1)	0

Source: Appendix 5.3.5.3.2.7 Table 65. Criterion for inclusion in this table = at least 1% incidence in a group for the SOC. SOC classes sorted by overall MenACWY frequency. [a]Total exposed vaccines.

Table 5.2.5-2 Summary of Probably or Possibly Related Unsolicited Adverse Events by MedDRA System Organ Class: MenACWY Alone Versus Menactra Across Geographic Regions: United States Versus Latin America, Ages 19 to 55

Unsolicited Adverse Events: MedDRA System Organ Class (SOC)	United States V59P13		Latin America V59P17	
	MenACWY Alone N=1018	Menactra N=336	MenACWY Alone N=1588	Menactra N=882
Any adverse event	71 (7)	17 (5)	147 (9)	80 (9)
General disorders & administration site conditions	37 (4)	6 (2)	60 (4)	20 (2)
Nervous system disorders	13 (1)	3 (1)	50 (3)	29 (3)
Musculoskeletal, connective tissue & bone disorders	11 (1)	1 (<1)	22 (1)	15 (2)
Gastrointestinal disorders	10 (1)	1 (<1)	17 (1)	14 (2)
Infections & infestations	4 (<1)	1 (<1)	23 (1)	11 (1)
Skin & subcutaneous tissue disorders	5 (<1)	1 (<1)	17 (1)	9 (1)
Blood & lymphatic system disorders	2 (<1)	1 (<1)	8 (1)	1 (<1)
Respiratory, thoracic & mediastinal disorders	5 (<1)	2 (1)	2 (<1)	3 (<1)

Source: Appendix 5.3.5.3.2.7 Table 66. Criterion for inclusion in this table = at least 1% incidence in the SOC. SOC sorted by overall MenACWY frequency.

5.2.2 Other Extrinsic Factors

No other extrinsic factors likely to influence the safety profiles of the vaccines were examined.

5.3 Drug Interactions

Potential vaccine-vaccine interactions were evaluated in studies of MenACWY alone compared with MenACWY given with routine concomitant vaccines and in a study of MenACWY alone and sequential administration of MenACWY given following Tdap and HPV.

As expected, in the 11 to 18 year age group, MenACWY given with concomitant Tdap or with Tdap and HPV (in-text Table 2.1.1.1.4-3) increased the incidence of local reactions and systemic reactions such as myalgia, arthralgia and malaise, which was reflective of the inherent reactogenicity of each of the vaccines administered. However, the severity of these reactions was not increased in comparison to MenACWY alone. MenACWY given sequentially after Tdap also increased the incidence but not the severity of myalgia (from 19% to 27%), arthralgia (from 11% to 17%), malaise (from 20 % to 24%), and analgesic/antypyretic use (from 13% to 19%). In contrast, MenACWY given sequentially after Tdap alone did not increase the incidence or severity of myalgia, arthralgia, malaise, analgesic/antipyretic use, or any other immediate reaction to vaccination. These reactions occurred relatively infrequently in the 11 to 18 age group and were considered to be of minimal clinical significance.

The incidence of all unsolicited AEs was low (no greater than 3% when MenACWY if given concomitantly with Tdap or Tdap + HPV), and no differences were noted in the incidence or severity of any AE (in-text Tables 2.1.1.2.1-2 and 2.1.1.2.2-1).

In conclusion, there was no evidence in the present investigations of vaccine-vaccine interactions when MenACWY was given concomitant with Tdap or with Tdap and HPV. There was also no evidence of vaccine-vaccine interaction when MenACWY was given 1 month after Tdap.

Use in Pregnancy and Lactation

Although the use of birth control measures, when appropriate, was an entry criterion for the studies, 34 women in studies V59P13 and V59P17 (please see CSRs V59P13, section 5.3.5.1.14 and V59P17, section 5.3.5.1.15) became pregnant during the 6-month follow-up period. Twenty-eight women were administered the MenACWY, and six women were administered Menactra. Table 5.4-1 lists the status of each pregnancy.

For 22 subjects, the pregnancy is ongoing, and the sponsor is monitoring the progression.

There have been four miscarriages, five therapeutic abortions, and one congenital anomaly. These outcomes were unrelated to study vaccines.

There have been two live births, and the sponsor is monitoring the health status of the children.

Table 5.4-1 Status of Pregnancies in Studies V59P13 and V59P17

Status of Pregnancy	MenACWY	Menactra	Total
Pregnancy ongoing (outcome pending)	18	4	22
Miscarriage	4	0	4
Therapeutic abortion	4	1	5
Live birth	2	0	2
Congenital anomaly	0	1	1

Source: Case report forms and pharmacovigilance database entries for each subject.

5.5 Overdose

Not applicable since a single dose of the study vaccines was administered.

5.6 Drug Abuse

Not applicable.

5.7 Withdrawal and Rebound

There is no evidence of rebound effects.

5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There is no evidence that MenACWY affects the ability to drive or use other machines.

6 Postmarketing Data

MenACWY has not been marketed in any region of the world.

7 Appendices

Agent: MenACWY

Table 1

Summary of Subject Populations, Number by Treatment within Study and Age Group

Age Group	Study	ACWY	ACWYConVax[4]	Total ACWY[5]	Menactra	Menomune	Tdap
11-18	V59P6[1]	151	0	151	0	209	0
	V59P11[2]	357	359	716	0	0	353
	V59P13	1631	0	1631	539	0	0
	V59P18[3]	541	540	1081	0	0	539
19-34	V59P13	307	0	307	105	0	0
	V59P17	838	0	838	464	0	0
35-55	V59P13	711	0	711	231	0	0
	V59P17	750	0	750	418	0	0
Total		5286	899	6185	1757	209	892

[1]Subjects from V59P6 who received adjuvanted MenACWY are excluded.
[2]Subjects ages 11-25.
[3]Subjects receiving MenACWY followed by Tdap are included under the MenACWY column here and for the Adverse Events observed during Month 1. Similarly, subjects receiving Tdap followed by MenACWY are included under the Tdap column. Subjects from V59P18 will not be included in the summaries of Adverse Events occurring during months 2 to 6. Data for the full duration of this period are not yet available because this study is still ongoing.
[4]Subjects in V59P11 received MenACWY+Tdap; Subjects in V59P18 received MenACWY+HPV+Tdap.
[5]All subjects who received either MenACWY alone or with a concomitant vaccine (column 1 + column 2).

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POPSUM.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1- popsum

Table 2

Summary of Demographics, Comparing Total MenACWY[1] across Age Groups

	Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
Age (Years):					
Mean	14.1	26.5	44.0	23.5	29.2
Median	14.0	26.0	44.0	17.0	27.0
Std. Dev.	2.4	4.5	5.7	12.9	13.4
Min	10	19	35	10	11
Max	25	34	55	55	55
N	3579	1145	1461	6185	1757
Sex:					
MALE	1784 (50%)	374 (33%)	382 (26%)	2540 (41%)	644 (37%)
FEMALE	1795 (50%)	771 (67%)	1079 (74%)	3645 (59%)	1113 (63%)
Race:					
ASIAN	49 (1%)	13 (1%)	25 (2%)	87 (1%)	26 (1%)
BLACK	140 (4%)	98 (9%)	119 (8%)	357 (6%)	186 (11%)
CAUCASIAN	2105 (59%)	372 (32%)	699 (48%)	3176 (51%)	810 (46%)
HISPANIC	1214 (34%)	654 (57%)	609 (42%)	2477 (40%)	707 (40%)
OTHER	71 (2%)	8 (<1%)	9 (<1%)	88 (1%)	28 (2%)
Weight (kg):					
Mean	57.68	68.23	74.78	63.68	67.59
Median	55.00	65.00	71.80	61.00	64.90
Std. Dev.	16.56	16.40	17.21	18.22	18.19
Min	21.8	36.0	41.0	21.8	25.5
Max	161.0	156.8	145.9	161.0	156.6
N	3577	1145	1461	6183	1757

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\DEMSUM_ACWY.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1- DEMSUM_ACWY

Table 2

Summary of Demographics, Comparing Total MenACWY[1] across Age Groups

	Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
Height (cm):					
Mean	161.26	165.86	164.39	162.86	163.38
Median	160.80	165.00	164.00	162.60	163.00
Std. Dev.	11.28	9.93	9.82	10.88	10.44
Min	121.9	134.6	137.2	121.9	114.0
Max	200.7	204.5	203.2	204.5	198.0
N	3573	1145	1461	6179	1757
Met Entry Criteria?:					
YES	3562 (100%)	1140 (100%)	1447 (99%)	6149 (99%)	1744 (99%)
NO	17 (<1%)	5 (<1%)	14 (<1%)	36 (<1%)	13 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\DEMSUM_ACWY.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1- DEMSUM_ACWY

Table 3.1

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 11-18

	ACWY (N=2680)	ACWYConVax (N=899)	Total ACWY (N=3579)	Menactra (N=539)	Menomune (N=209)	Tdap (N=892)
Age (Years):						
Mean	14.1	14.1	14.1	14.0	14.2	13.9
Median	14.0	13.0	14.0	14.0	14.0	13.0
Std. Dev.	2.3	2.7	2.4	2.2	1.8	2.6
Min	11	10	10	11	11	11
Max	25	25	25	18	17	25
N	2680	899	3579	539	209	892
Sex:						
MALE	1380 (51%)	404 (45%)	1784 (50%)	289 (54%)	128 (61%)	422 (47%)
FEMALE	1300 (49%)	495 (55%)	1795 (50%)	250 (46%)	81 (39%)	470 (53%)
Race:						
ASIAN	48 (2%)	1 (<1%)	49 (1%)	17 (3%)	1 (<1%)	1 (<1%)
BLACK	138 (5%)	2 (<1%)	140 (4%)	45 (8%)	3 (1%)	1 (<1%)
CAUCASIAN	1757 (66%)	348 (39%)	2105 (59%)	422 (78%)	193 (92%)	345 (39%)
HISPANIC	671 (25%)	543 (60%)	1214 (34%)	34 (6%)	1 (<1%)	543 (61%)
OTHER	66 (2%)	5 (<1%)	71 (2%)	21 (4%)	11 (5%)	2 (<1%)
Weight (kg):						
Mean	58.69	54.69	57.68	60.09	62.45	53.89
Median	56.00	53.00	55.00	57.30	59.90	52.35
Std. Dev.	17.38	13.37	16.56	18.59	18.42	13.52
Min	21.8	27.2	21.8	25.5	28.2	24.0
Max	161.0	120.0	161.0	152.3	133.2	128.5
N	2678	899	3577	539	209	892

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\DEMSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1- DEMSUM_TRT_11_18

Table 3.1

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 11-18

	ACWY (N=2680)	ACWYConVax (N=899)	Total ACWY (N=3579)	Menactra (N=539)	Menomune (N=209)	Tdap (N=892)
Height (cm):						
Mean	161.81	159.63	161.26	162.45	165.78	159.17
Median	161.30	159.50	160.80	162.60	166.40	159.00
Std. Dev.	11.58	10.16	11.28	11.77	11.30	10.18
Min	121.9	130.0	121.9	119.4	133.6	129.0
Max	200.7	197.0	200.7	195.6	190.5	185.0
N	2674	899	3573	539	209	892
Met Entry Criteria?:						
YES	2664 (99%)	898 (100%)	3562 (100%)	534 (99%)	209 (100%)	891 (100%)
NO	16 (<1%)	1 (<1%)	17 (<1%)	5 (<1%)	0	1 (<1%)

Table 3.2

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 19-34

	ACWY (N=1145)	Menactra (N=569)
Age (Years):		
Mean	26.5	26.2
Median	26.0	26.0
Std. Dev.	4.5	4.5
Min	19	19
Max	34	34
N	1145	569
Sex:		
MALE	374 (33%)	200 (35%)
FEMALE	771 (67%)	369 (65%)
Race:		
ASIAN	13 (1%)	7 (1%)
BLACK	98 (9%)	69 (12%)
CAUCASIAN	372 (32%)	144 (25%)
HISPANIC	654 (57%)	347 (61%)
OTHER	8 (<1%)	2 (<1%)
Weight (kg):		
Mean	68.23	68.38
Median	65.00	65.00
Std. Dev.	16.40	16.72
Min	36.0	39.3
Max	156.8	156.6
N	1145	569

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\DEMSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1- DEMSUM_TRT_19_34

Table 3.2

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 19-34

	ACWY (N=1145)	Menactra (N=569)
Height (cm):		
Mean	165.86	165.53
Median	165.00	165.00
Std. Dev.	9.93	9.49
Min	134.6	137.0
Max	204.5	198.0
N	1145	569
Met Entry Criteria?:		
YES	1140 (100%)	568 (100%)
NO	5 (<1%)	1 (<1%)

Table 3.3

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 35-55

	ACWY (N=1461)	Menactra (N=649)
Age (Years):		
Mean	44.0	44.3
Median	44.0	44.0
Std. Dev.	5.7	5.8
Min	35	35
Max	55	55
N	1461	649
Sex:		
MALE	382 (26%)	155 (24%)
FEMALE	1079 (74%)	494 (76%)
Race:		
ASIAN	25 (2%)	2 (<1%)
BLACK	119 (8%)	72 (11%)
CAUCASIAN	699 (48%)	244 (38%)
HISPANIC	609 (42%)	326 (50%)
OTHER	9 (<1%)	5 (<1%)
Weight (kg):		
Mean	74.78	73.13
Median	71.80	69.80
Std. Dev.	17.21	16.92
Min	41.0	39.5
Max	145.9	155.0
N	1461	649

Table 3.3

Summary of Demographics, Comparing Treatment within Age Group
Subjects Ages 35-55

	ACWY (N=1461)	Menactra (N=649)
Height (cm):		
Mean	164.39	162.28
Median	164.00	162.00
Std. Dev.	9.82	9.77
Min	137.2	114.0
Max	203.2	190.5
N	1461	649
Met Entry Criteria?:		
YES	1447 (99%)	642 (99%)
NO	14 (<1%)	7 (1%)

Table 4

Summary of Reasons for Withdrawal from Study, Comparing Total MenACWY[1] across Age Groups

Primary Withdrawal Reason	Number of Subjects (% of Total)				
	Ages 11-18	Ages 19-34	Ages 35-55	Total ACWY	Total Menactra
TOTAL NUMBER OF SUBJECTS ENROLLED	3579	1145	1461	6185	1757
ONGOING	996 (28%)	0	0	996 (16%)	0
COMPLETED	2446 (68%)	1124 (98%)	1454 (100%)	5024 (81%)	1731 (99%)
COMPLETED PROTOCOL	2446 (68%)	1124 (98%)	1454 (100%)	5024 (81%)	1731 (99%)
PREMATURE WITHDRAWAL	137 (4%)	21 (2%)	7 (< 1%)	165 (3%)	26 (1%)
AE OR DEATH	1 (< 1%)	0	0	1 (< 1%)	0
WITHDRAWAL OF CONSENT	60 (2%)	0	0	60 (< 1%)	3 (< 1%)
LOST TO FOLLOW-UP	61 (2%)	21 (2%)	7 (< 1%)	89 (1%)	21 (1%)
INAPPROPRIATE ENROLLMENT	1 (< 1%)	0	0	1 (< 1%)	0
ADMINISTRATIVE REASON	2 (< 1%)	0	0	2 (< 1%)	0
PROTOCOL DEVIATION/VIOLATION	10 (< 1%)	0	0	10 (< 1%)	2 (< 1%)
UNABLE TO CLASSIFY	2 (< 1%)	0	0	2 (< 1%)	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\TSSUM_ACWY.SAS(WARTERO) 10JUL08, 09:01 SAS.9.1 TSSUM_ACWY

Table 5.1

Summary of Reasons for Withdrawal from Study, Comparing Treatment within Age Group
Subjects Ages 11-18

Primary Withdrawal Reason	Number of Subjects (% of Total)					
	ACWY	ACWYConVax	Total ACWY	Menactra	Menomune	Tdap
TOTAL NUMBER OF SUBJECTS ENROLLED	2680	899	3579	539	209	892
ONGOING	495 (18%)	501 (56%)	996 (28%)	0	0	488 (55%)
COMPLETED	2094 (78%)	352 (39%)	2446 (68%)	524 (97%)	203 (97%)	349 (39%)
COMPLETED PROTOCOL	2094 (78%)	352 (39%)	2446 (68%)	524 (97%)	203 (97%)	349 (39%)
PREMATURE WITHDRAWAL	91 (3%)	46 (5%)	137 (4%)	15 (3%)	6 (3%)	55 (6%)
AE OR DEATH	0	1 (< 1%)	1 (< 1%)	0	0	0
WITHDRAWAL OF CONSENT	36 (1%)	24 (3%)	60 (2%)	2 (< 1%)	1 (< 1%)	31 (3%)
LOST TO FOLLOW-UP	47 (2%)	14 (2%)	61 (2%)	12 (2%)	5 (2%)	19 (2%)
INAPPROPRIATE ENROLLMENT	1 (< 1%)	0	1 (< 1%)	0	0	0
ADMINISTRATIVE REASON	2 (< 1%)	0	2 (< 1%)	0	0	2 (< 1%)
PROTOCOL DEVIATION/VIOLATION	5 (< 1%)	5 (< 1%)	10 (< 1%)	1 (< 1%)	0	1 (< 1%)
UNABLE TO CLASSIFY	0	2 (< 1%)	2 (< 1%)	0	0	2 (< 1%)

Table 5.2

Summary of Reasons for Withdrawal from Study, Comparing Treatment within Age Group
Subjects Ages 19-34

Primary Withdrawal Reason	Number of Subjects (% of Total) ACWY	Menactra
TOTAL NUMBER OF SUBJECTS ENROLLED	1145	569
COMPLETED	1124 (98%)	563 (99%)
COMPLETED PROTOCOL	1124 (98%)	563 (99%)
PREMATURE WITHDRAWAL	21 (2%)	6 (1%)
WITHDRAWAL OF CONSENT	0	1 (< 1%)
LOST TO FOLLOW-UP	21 (2%)	5 (< 1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\TSSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 09:02 SAS.9.1 TSSUM_TRT_19_34

Table 5.3

Summary of Reasons for Withdrawal from Study, Comparing Treatment within Age Group
Subjects Ages 35-55

Primary Withdrawal Reason	Number of Subjects (% of Total) ACWY	Menactra
TOTAL NUMBER OF SUBJECTS ENROLLED	1461	649
COMPLETED	1454 (100%)	644 (99%)
COMPLETED PROTOCOL	1454 (100%)	644 (99%)
PREMATURE WITHDRAWAL	7 (< 1%)	5 (< 1%)
LOST TO FOLLOW-UP	7 (< 1%)	4 (< 1%)
PROTOCOL DEVIATION/VIOLATION	0	1 (< 1%)

Table 6

Summary of Subjects With At Least One Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects				
		Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
Any	ANY	2406 (67%)	743 (65%)	817 (56%)	3966 (64%)	1146 (65%)
	MISSING	6 (<1%)	0	0	6 (<1%)	0
	NONE	1167 (33%)	402 (35%)	644 (44%)	2213 (36%)	611 (35%)
Local	ANY	1739 (49%)	590 (52%)	605 (41%)	2934 (47%)	906 (52%)
	MISSING	7 (<1%)	0	0	7 (<1%)	0
	NONE	1833 (51%)	555 (48%)	856 (59%)	3244 (52%)	851 (48%)
Systemic	ANY	1748 (49%)	460 (40%)	532 (36%)	2740 (44%)	725 (41%)
	MISSING	6 (<1%)	0	0	6 (<1%)	0
	NONE	1825 (51%)	685 (60%)	929 (64%)	3439 (56%)	1032 (59%)
Other	ANY	657 (18%)	225 (20%)	298 (20%)	1180 (19%)	345 (20%)
	MISSING	6 (<1%)	0	0	6 (<1%)	1 (<1%)
	NONE	2916 (81%)	920 (80%)	1163 (80%)	4999 (81%)	1411 (80%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJOVW_ACWY

Table 7.1

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
Any	ANY	127 (84%)	160 (77%)	221 (62%)	302 (86%)	1044 (64%)	379 (70%)	373 (69%)	443 (82%)
	MISSING	0	0	0	0	6 (<1%)	0	0	0
	NONE	24 (16%)	49 (23%)	136 (38%)	51 (14%)	581 (36%)	160 (30%)	168 (31%)	96 (18%)
Local	ANY	107 (71%)	126 (60%)	153 (43%)	264 (75%)	809 (50%)	313 (58%)	279 (52%)	399 (74%)
	MISSING	0	0	0	0	7 (<1%)	0	0	0
	NONE	44 (29%)	83 (40%)	204 (57%)	89 (25%)	815 (50%)	226 (42%)	262 (48%)	140 (26%)
Systemic	ANY	85 (56%)	102 (49%)	171 (48%)	202 (57%)	710 (44%)	234 (43%)	274 (51%)	309 (57%)
	MISSING	0	0	0	0	6 (<1%)	0	0	0
	NONE	66 (44%)	107 (51%)	186 (52%)	151 (43%)	915 (56%)	305 (57%)	267 (49%)	230 (43%)
Other	ANY	40 (26%)	59 (28%)	33 (9%)	39 (11%)	312 (19%)	108 (20%)	97 (18%)	112 (21%)
	MISSING	0	0	0	0	6 (<1%)	0	0	0
	NONE	111 (74%)	150 (72%)	324 (91%)	314 (89%)	1313 (81%)	431 (80%)	444 (82%)	427 (79%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_11_18.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINOVW_MEN_VS_CONTROL_11_18

Table 7.2

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects			
		P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
Any	ANY	211 (69%)	63 (60%)	532 (63%)	299 (64%)
	NONE	96 (31%)	42 (40%)	306 (37%)	165 (36%)
Local	ANY	176 (57%)	48 (46%)	414 (49%)	248 (53%)
	NONE	131 (43%)	57 (54%)	424 (51%)	216 (47%)
Systemic	ANY	129 (42%)	36 (34%)	331 (39%)	196 (42%)
	NONE	178 (58%)	69 (66%)	507 (61%)	268 (58%)
Other	ANY	65 (21%)	20 (19%)	160 (19%)	72 (16%)
	NONE	242 (79%)	85 (81%)	678 (81%)	392 (84%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_19_34.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINOVW_MEN_VS_CONTROL_19_34

Table 7.3

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects			
		P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
Any	ANY	394 (55%)	143 (62%)	423 (56%)	262 (63%)
	NONE	317 (45%)	88 (38%)	327 (44%)	156 (37%)
Local	ANY	290 (41%)	106 (46%)	315 (42%)	191 (46%)
	NONE	421 (59%)	125 (54%)	435 (58%)	227 (54%)
Systemic	ANY	247 (35%)	80 (35%)	285 (38%)	179 (43%)
	NONE	464 (65%)	151 (65%)	465 (62%)	239 (57%)
Other	ANY	178 (25%)	55 (24%)	120 (16%)	90 (22%)
	MISSING	0	0	0	1 (<1%)
	NONE	533 (75%)	176 (76%)	630 (84%)	327 (78%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_35_55.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINOVW_MEN_VS_CONTROL_35_55

Table 8

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
Any	ANY	127 (84%)	221 (62%)	236 (66%)	1044 (64%)	373 (69%)	405 (75%)
	MISSING	0	0	0	6 (<1%)	0	0
	NONE	24 (16%)	136 (38%)	123 (34%)	581 (36%)	168 (31%)	135 (25%)
Local	ANY	107 (71%)	153 (43%)	102 (28%)	809 (50%)	279 (52%)	289 (54%)
	MISSING	0	0	0	7 (<1%)	0	0
	NONE	44 (29%)	204 (57%)	257 (72%)	815 (50%)	262 (48%)	251 (46%)
Systemic	ANY	85 (56%)	171 (48%)	198 (55%)	710 (44%)	274 (51%)	310 (57%)
	MISSING	0	0	0	6 (<1%)	0	0
	NONE	66 (44%)	186 (52%)	161 (45%)	915 (56%)	267 (49%)	230 (43%)
Other	ANY	40 (26%)	33 (9%)	42 (12%)	312 (19%)	97 (18%)	133 (25%)
	MISSING	0	0	0	6 (<1%)	0	0
	NONE	111 (74%)	324 (91%)	317 (88%)	1313 (81%)	444 (82%)	407 (75%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINOVW_MEN_VS_CONVAC_11_18

Table 9

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
Any	ANY	127 (84%)	221 (62%)	1044 (64%)	373 (69%)	322 (64%)
	MISSING	0	0	6 (<1%)	0	0
	NONE	24 (16%)	136 (38%)	581 (36%)	168 (31%)	181 (36%)
Local	ANY	107 (71%)	153 (43%)	809 (50%)	279 (52%)	260 (52%)
	MISSING	0	0	7 (<1%)	0	0
	NONE	44 (29%)	204 (57%)	815 (50%)	262 (48%)	243 (48%)
Systemic	ANY	85 (56%)	171 (48%)	710 (44%)	274 (51%)	215 (43%)
	MISSING	0	0	6 (<1%)	0	0
	NONE	66 (44%)	186 (52%)	915 (56%)	267 (49%)	288 (57%)
Other	ANY	40 (26%)	33 (9%)	312 (19%)	97 (18%)	67 (13%)
	MISSING	0	0	6 (<1%)	0	0
	NONE	111 (74%)	324 (91%)	1313 (81%)	444 (82%)	436 (87%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINOVW_MEN_VS_TDAP_11_18

Table 10

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups

	Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
Any Reaction:					
NONE	1210 (34%)	410 (36%)	665 (46%)	2285 (37%)	630 (36%)
OTHER THAN SEVERE	2043 (57%)	648 (57%)	696 (48%)	3387 (55%)	1017 (58%)
SEVERE*	320 (9%)	87 (8%)	100 (7%)	507 (8%)	110 (6%)
MISSING	6 (<1%)	0	0	6 (<1%)	0
Local:					
NONE	1833 (51%)	555 (48%)	856 (59%)	3244 (52%)	851 (48%)
MILD	1607 (45%)	550 (48%)	552 (38%)	2709 (44%)	852 (48%)
SEVERE OR > 50MM*	132 (4%)	40 (3%)	53 (4%)	225 (4%)	54 (3%)
MISSING	7 (<1%)	0	0	7 (<1%)	0
Systemic:					
NONE	1838 (51%)	694 (61%)	938 (64%)	3470 (56%)	1048 (60%)
OTHER THAN SEVERE	1502 (42%)	395 (34%)	457 (31%)	2354 (38%)	639 (36%)
SEVERE*	233 (7%)	56 (5%)	66 (5%)	355 (6%)	70 (4%)
MISSING	6 (<1%)	0	0	6 (<1%)	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.
*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_ACWY.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_ACWY

Table 11.1

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

	P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
Any Reaction:								
NONE	25 (17%)	51 (24%)	137 (38%)	51 (14%)	605 (37%)	169 (31%)	174 (32%)	99 (18%)
OTHER THAN SEVERE	112 (74%)	149 (71%)	184 (52%)	261 (74%)	905 (55%)	344 (64%)	317 (59%)	381 (71%)
SEVERE*	14 (9%)	9 (4%)	36 (10%)	41 (12%)	115 (7%)	26 (5%)	50 (9%)	59 (11%)
MISSING	0	0	0	0	6 (<1%)	0	0	0
Local:								
NONE	44 (29%)	83 (40%)	204 (57%)	89 (25%)	815 (50%)	226 (42%)	262 (48%)	140 (26%)
MILD	100 (66%)	123 (59%)	139 (39%)	241 (68%)	747 (46%)	299 (55%)	262 (48%)	361 (67%)
SEVERE OR > 50MM*	7 (5%)	3 (1%)	14 (4%)	23 (7%)	62 (4%)	14 (3%)	17 (3%)	38 (7%)
MISSING	0	0	0	0	7 (<1%)	0	0	0
Systemic:								
NONE	66 (44%)	107 (51%)	186 (52%)	151 (43%)	926 (57%)	313 (58%)	268 (50%)	233 (43%)
OTHER THAN SEVERE	76 (50%)	96 (46%)	143 (40%)	179 (51%)	632 (39%)	213 (40%)	235 (43%)	269 (50%)
SEVERE*	9 (6%)	6 (3%)	28 (8%)	23 (7%)	67 (4%)	13 (2%)	38 (7%)	37 (7%)
MISSING	0	0	0	0	6 (<1%)	0	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MEN_VS_CONT_11_18.SAS(WARTERO) 11JUL08, 01:01 SAS.9.1- PINOVW_SEV_MEN_VS_CONT_11_18

Table 11.2

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

	P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
Any Reaction:				
NONE	98 (32%)	44 (42%)	312 (37%)	166 (36%)
OTHER THAN SEVERE	192 (63%)	55 (52%)	456 (54%)	265 (57%)
SEVERE*	17 (6%)	6 (6%)	70 (8%)	33 (7%)
Local:				
NONE	131 (43%)	57 (54%)	424 (51%)	216 (47%)
MILD	165 (54%)	48 (46%)	385 (46%)	228 (49%)
SEVERE OR > 50MM*	11 (4%)	0	29 (3%)	20 (4%)
Systemic:				
NONE	181 (59%)	69 (66%)	513 (61%)	272 (59%)
OTHER THAN SEVERE	118 (38%)	30 (29%)	277 (33%)	175 (38%)
SEVERE*	8 (3%)	6 (6%)	48 (6%)	17 (4%)

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MEN_VS_CONT_19_34.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MEN_VS_CONT_19_34

Table 11.3

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

	P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
Any Reaction:				
NONE	335 (47%)	92 (40%)	330 (44%)	159 (38%)
OTHER THAN SEVERE	341 (48%)	131 (57%)	355 (47%)	222 (53%)
SEVERE*	35 (5%)	8 (3%)	65 (9%)	37 (9%)
Local:				
NONE	421 (59%)	125 (54%)	435 (58%)	227 (54%)
MILD	268 (38%)	103 (45%)	284 (38%)	174 (42%)
SEVERE OR > 50MM*	22 (3%)	3 (1%)	31 (4%)	17 (4%)
Systemic:				
NONE	470 (66%)	152 (66%)	468 (62%)	242 (58%)
OTHER THAN SEVERE	222 (31%)	74 (32%)	235 (31%)	147 (35%)
SEVERE*	19 (3%)	5 (2%)	47 (6%)	29 (7%)

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MEN_VS_CONT_35_55.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MEN_VS_CONT_35_55

Table 12

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

	P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
Any Reaction:						
NONE	25 (17%)	137 (38%)	125 (35%)	605 (37%)	174 (32%)	144 (27%)
OTHER THAN SEVERE	112 (74%)	184 (52%)	192 (53%)	905 (55%)	317 (59%)	333 (62%)
SEVERE*	14 (9%)	36 (10%)	42 (12%)	115 (7%)	50 (9%)	63 (12%)
MISSING	0	0	0	6 (<1%)	0	0
Local:						
NONE	44 (29%)	204 (57%)	257 (72%)	815 (50%)	262 (48%)	251 (46%)
MILD	100 (66%)	139 (39%)	96 (27%)	747 (46%)	262 (48%)	263 (49%)
SEVERE OR > 50MM*	7 (5%)	14 (4%)	6 (2%)	62 (4%)	17 (3%)	26 (5%)
MISSING	0	0	0	7 (<1%)	0	0
Systemic:						
NONE	66 (44%)	186 (52%)	161 (45%)	926 (57%)	268 (50%)	231 (43%)
OTHER THAN SEVERE	76 (50%)	143 (40%)	157 (44%)	632 (39%)	235 (43%)	259 (48%)
SEVERE*	9 (6%)	28 (8%)	41 (11%)	67 (4%)	38 (7%)	50 (9%)
MISSING	0	0	0	6 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1- PINOVW_SEV_MEN_VS_CONVAC_11_18

Table 13

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

	P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
Any Reaction:					
NONE	25 (17%)	137 (38%)	605 (37%)	174 (32%)	187 (37%)
OTHER THAN SEVERE	112 (74%)	184 (52%)	905 (55%)	317 (59%)	275 (55%)
SEVERE*	14 (9%)	36 (10%)	115 (7%)	50 (9%)	41 (8%)
MISSING	0	0	6 (<1%)	0	0
Local:					
NONE	44 (29%)	204 (57%)	815 (50%)	262 (48%)	243 (48%)
MILD	100 (66%)	139 (39%)	747 (46%)	262 (48%)	241 (48%)
SEVERE OR > 50MM*	7 (5%)	14 (4%)	62 (4%)	17 (3%)	19 (4%)
MISSING	0	0	7 (<1%)	0	0
Systemic:					
NONE	66 (44%)	186 (52%)	926 (57%)	268 (50%)	289 (57%)
OTHER THAN SEVERE	76 (50%)	143 (40%)	632 (39%)	235 (43%)	181 (36%)
SEVERE*	9 (6%)	28 (8%)	67 (4%)	38 (7%)	33 (7%)
MISSING	0	0	6 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1- PINOVW_SEV_MEN_VS_TDAP_11_18

Table 14

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
INJECTION SITE						
Pain	N	3571	1145	1461	6177	1757
	ANY	1501 (42%)	510 (45%)	513 (35%)	2524 (41%)	816 (46%)
	MILD	1084 (30%)	380 (33%)	374 (26%)	1838 (30%)	603 (34%)
	MODERATE	361 (10%)	111 (10%)	114 (8%)	586 (9%)	177 (10%)
	SEVERE	56 (2%)	19 (2%)	25 (2%)	100 (2%)	36 (2%)
Erythema (mm)	N	3572	1145	1461	6178	1757
	ANY	552 (15%)	192 (17%)	182 (12%)	926 (15%)	231 (13%)
	>0 - 25 mm	446 (12%)	156 (14%)	138 (9%)	740 (12%)	193 (11%)
	>25 - 50 mm	54 (2%)	16 (1%)	19 (1%)	89 (1%)	21 (1%)
	> 50 mm	52 (1%)	20 (2%)	25 (2%)	97 (2%)	17 (1%)
Induration (mm)	N	3572	1145	1461	6178	1757
	ANY	468 (13%)	150 (13%)	157 (11%)	775 (13%)	203 (12%)
	>0 - 25 mm	339 (9%)	120 (10%)	126 (9%)	585 (9%)	163 (9%)
	>25 - 50 mm	70 (2%)	16 (1%)	18 (1%)	104 (2%)	25 (1%)
	> 50 mm	59 (2%)	14 (1%)	13 (1%)	86 (1%)	15 (1%)
SYSTEMIC						
Chills	N	3573	1145	1461	6179	1757
	ANY	380 (11%)	79 (7%)	86 (6%)	545 (9%)	120 (7%)
	MILD	252 (7%)	51 (4%)	52 (4%)	355 (6%)	84 (5%)
	MODERATE	95 (3%)	17 (1%)	25 (2%)	137 (2%)	30 (2%)
	SEVERE	33 (1%)	11 (1%)	9 (1%)	53 (1%)	6 (<1%)
Nausea	N	3573	1145	1461	6179	1757
	ANY	440 (12%)	97 (8%)	88 (6%)	625 (10%)	142 (8%)
	MILD	293 (8%)	69 (6%)	64 (4%)	426 (7%)	97 (6%)
	MODERATE	114 (3%)	20 (2%)	18 (1%)	152 (2%)	36 (2%)
	SEVERE	33 (1%)	8 (1%)	6 (<1%)	47 (1%)	9 (1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJSUM_ACWY

Table 14

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Malaise	N	3573	1145	1461	6179	1757
	ANY	550 (15%)	205 (18%)	206 (14%)	961 (16%)	285 (16%)
	MILD	326 (9%)	131 (11%)	119 (8%)	576 (9%)	175 (10%)
	MODERATE	169 (5%)	44 (4%)	65 (4%)	278 (4%)	88 (5%)
	SEVERE	55 (2%)	30 (3%)	22 (2%)	107 (2%)	22 (1%)
Myalgia	N	3573	1145	1461	6179	1757
	ANY	791 (22%)	160 (14%)	179 (12%)	1130 (18%)	280 (16%)
	MILD	519 (15%)	106 (9%)	108 (7%)	733 (12%)	180 (10%)
	MODERATE	198 (6%)	38 (3%)	57 (4%)	293 (5%)	83 (5%)
	SEVERE	74 (2%)	16 (1%)	14 (1%)	104 (2%)	17 (1%)
Arthralgia	N	3573	1145	1461	6179	1757
	ANY	402 (11%)	74 (6%)	104 (7%)	580 (9%)	130 (7%)
	MILD	266 (7%)	52 (5%)	63 (4%)	381 (6%)	84 (5%)
	MODERATE	95 (3%)	16 (1%)	27 (2%)	138 (2%)	36 (2%)
	SEVERE	41 (1%)	6 (1%)	14 (1%)	61 (1%)	10 (1%)
Headache	N	3573	1145	1461	6179	1757
	ANY	1207 (34%)	316 (28%)	358 (25%)	1881 (30%)	491 (28%)
	MILD	748 (21%)	203 (18%)	231 (16%)	1182 (19%)	320 (18%)
	MODERATE	321 (9%)	86 (8%)	89 (6%)	496 (8%)	133 (8%)
	SEVERE	138 (4%)	27 (2%)	38 (3%)	203 (3%)	38 (2%)
Rash	N	2706	1145	1461	5312	1757
	ANY	82 (3%)	39 (3%)	39 (3%)	160 (3%)	42 (2%)
	OTHER	22 (1%)	11 (1%)	10 (1%)	43 (1%)	15 (1%)
	URTICARIAL	60 (2%)	28 (2%)	29 (2%)	117 (2%)	27 (2%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJSUM_ACWY

Table 14

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Fever (>= 38C)	N	3564	1145	1458	6167	1754
	YES	96 (3%)	31 (3%)	34 (2%)	161 (3%)	37 (2%)
	NO	3468 (97%)	1114 (97%)	1424 (98%)	6006 (97%)	1717 (98%)
OTHER						
Stayed Home	N	3498	1133	1458	6089	1745
	YES	176 (5%)	47 (4%)	45 (3%)	268 (4%)	63 (4%)
	NO	3322 (95%)	1086 (96%)	1413 (97%)	5821 (96%)	1682 (96%)
Analgesic Antipyretics	N	3573	1145	1461	6179	1756
	YES	576 (16%)	208 (18%)	282 (19%)	1066 (17%)	326 (19%)
	NO	2997 (84%)	937 (82%)	1179 (81%)	5113 (83%)	1430 (81%)
Temperature (C)	N	3564	1145	1458	6167	1754
	<38 C	3468 (97%)	1114 (97%)	1424 (98%)	6006 (97%)	1717 (98%)
	38 - 38.9 C	77 (2%)	21 (2%)	27 (2%)	125 (2%)	27 (2%)
	39.0 - 39.9 C	17 (<1%)	8 (1%)	5 (<1%)	30 (<1%)	8 (<1%)
	>= 40 C	2 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJSUM_ACWY

Table 15.1

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
INJECTION SITE									
Pain	N	151	209	357	353	1623	539	541	539
	ANY	81 (54%)	114 (55%)	116 (32%)	246 (70%)	714 (44%)	287 (53%)	245 (45%)	383 (71%)
	MILD	67 (44%)	88 (42%)	72 (20%)	134 (38%)	560 (35%)	219 (41%)	162 (30%)	214 (40%)
	MODERATE	14 (9%)	24 (11%)	34 (10%)	95 (27%)	138 (9%)	61 (11%)	75 (14%)	140 (26%)
	SEVERE	0	2 (1%)	10 (3%)	17 (5%)	16 (1%)	7 (1%)	8 (1%)	29 (5%)
Erythema (mm)	N	151	209	357	353	1624	539	541	539
	ANY	57 (38%)	39 (19%)	66 (18%)	103 (29%)	247 (15%)	85 (16%)	66 (12%)	70 (13%)
	>0 - 25 mm	48 (32%)	38 (18%)	58 (16%)	87 (25%)	180 (11%)	70 (13%)	60 (11%)	65 (12%)
	>25 - 50 mm	4 (3%)	1 (<1%)	7 (2%)	13 (4%)	31 (2%)	8 (1%)	3 (1%)	4 (1%)
	> 50 mm	5 (3%)	0	1 (<1%)	3 (1%)	36 (2%)	7 (1%)	3 (1%)	1 (<1%)
Induration (mm)	N	151	209	357	353	1624	539	541	539
	ANY	34 (23%)	23 (11%)	59 (17%)	118 (33%)	196 (12%)	59 (11%)	70 (13%)	109 (20%)
	>0 - 25 mm	24 (16%)	22 (11%)	45 (13%)	80 (23%)	135 (8%)	45 (8%)	56 (10%)	80 (15%)
	>25 - 50 mm	4 (3%)	0	10 (3%)	32 (9%)	30 (2%)	10 (2%)	8 (1%)	20 (4%)
	> 50 mm	6 (4%)	1 (<1%)	4 (1%)	6 (2%)	31 (2%)	4 (1%)	6 (1%)	9 (2%)
SYSTEMIC									
Chills	N	151	209	357	353	1625	539	541	539
	ANY	24 (16%)	16 (8%)	47 (13%)	41 (12%)	127 (8%)	38 (7%)	66 (12%)	70 (13%)
	MILD	17 (11%)	12 (6%)	29 (8%)	31 (9%)	88 (5%)	29 (5%)	42 (8%)	51 (9%)
	MODERATE	5 (3%)	3 (1%)	12 (3%)	7 (2%)	30 (2%)	8 (1%)	18 (3%)	17 (3%)
	SEVERE	2 (1%)	1 (<1%)	6 (2%)	3 (1%)	9 (1%)	1 (<1%)	6 (1%)	2 (<1%)
Nausea	N	151	209	357	353	1625	539	541	539
	ANY	22 (15%)	20 (10%)	28 (8%)	35 (10%)	187 (12%)	47 (9%)	72 (13%)	82 (15%)
	MILD	15 (10%)	14 (7%)	17 (5%)	25 (7%)	122 (8%)	30 (6%)	45 (8%)	56 (10%)
	MODERATE	5 (3%)	4 (2%)	7 (2%)	8 (2%)	55 (3%)	13 (2%)	23 (4%)	24 (4%)
	SEVERE	2 (1%)	2 (1%)	4 (1%)	2 (1%)	10 (1%)	4 (1%)	4 (1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_11_18.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_11_18

Table 15.1

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
SYSTEMIC									
Malaise	N	151	209	357	353	1625	539	541	539
	ANY	23 (15%)	21 (10%)	43 (12%)	57 (16%)	177 (11%)	65 (12%)	110 (20%)	115 (21%)
	MILD	13 (9%)	13 (6%)	23 (6%)	40 (11%)	105 (6%)	34 (6%)	71 (13%)	66 (12%)
	MODERATE	7 (5%)	7 (3%)	15 (4%)	12 (3%)	56 (3%)	26 (5%)	32 (6%)	43 (8%)
	SEVERE	3 (2%)	1 (<1%)	5 (1%)	5 (1%)	16 (1%)	5 (1%)	7 (1%)	6 (1%)
Myalgia	N	151	209	357	353	1625	539	541	539
	ANY	35 (23%)	30 (14%)	79 (22%)	127 (36%)	310 (19%)	99 (18%)	104 (19%)	141 (26%)
	MILD	28 (19%)	19 (9%)	46 (13%)	81 (23%)	223 (14%)	68 (13%)	67 (12%)	88 (16%)
	MODERATE	6 (4%)	11 (5%)	24 (7%)	37 (10%)	63 (4%)	29 (5%)	30 (6%)	42 (8%)
	SEVERE	1 (1%)	0	9 (3%)	9 (3%)	24 (1%)	2 (<1%)	7 (1%)	11 (2%)
Arthralgia	N	151	209	357	353	1625	539	541	539
	ANY	12 (8%)	7 (3%)	40 (11%)	60 (17%)	137 (8%)	34 (6%)	62 (11%)	76 (14%)
	MILD	12 (8%)	3 (1%)	24 (7%)	35 (10%)	102 (6%)	27 (5%)	40 (7%)	48 (9%)
	MODERATE	0	4 (2%)	7 (2%)	21 (6%)	28 (2%)	7 (1%)	19 (4%)	22 (4%)
	SEVERE	0	0	9 (3%)	4 (1%)	7 (<1%)	0	3 (1%)	6 (1%)
Headache	N	151	209	357	353	1625	539	541	539
	ANY	62 (41%)	82 (39%)	128 (36%)	110 (31%)	478 (29%)	153 (28%)	194 (36%)	200 (37%)
	MILD	42 (28%)	54 (26%)	82 (23%)	76 (22%)	322 (20%)	107 (20%)	101 (19%)	119 (22%)
	MODERATE	13 (9%)	23 (11%)	27 (8%)	23 (7%)	123 (8%)	39 (7%)	70 (13%)	57 (11%)
	SEVERE	7 (5%)	5 (2%)	19 (5%)	11 (3%)	33 (2%)	7 (1%)	23 (4%)	24 (4%)
Rash	N	0	0	0	0	1625	539	541	539
	ANY	0	0	0	0	44 (3%)	18 (3%)	17 (3%)	20 (4%)
	OTHER	0	0	0	0	21 (1%)	8 (1%)	1 (<1%)	3 (1%)
	URTICARIAL	0	0	0	0	23 (1%)	10 (2%)	16 (3%)	17 (3%)
Fever (>= 38C)	N	151	209	357	353	1616	536	541	539
	YES	1 (1%)	4 (2%)	14 (4%)	7 (2%)	23 (1%)	4 (1%)	19 (4%)	17 (3%)
	NO	150 (99%)	205 (98%)	343 (96%)	346 (98%)	1593 (99%)	532 (99%)	522 (96%)	522 (97%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_11_18.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_11_18

Table 15.1

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
OTHER									
Stayed Home	N	150	209	357	353	1611	532	509	502
	YES	6 (4%)	4 (2%)	12 (3%)	15 (4%)	52 (3%)	14 (3%)	40 (8%)	39 (8%)
	NO	144 (96%)	205 (98%)	345 (97%)	338 (96%)	1559 (97%)	518 (97%)	469 (92%)	463 (92%)
Analgesic Antipyretics	N	151	209	357	353	1625	539	541	539
	YES	39 (26%)	59 (28%)	31 (9%)	38 (11%)	293 (18%)	104 (19%)	73 (13%)	92 (17%)
	NO	112 (74%)	150 (72%)	326 (91%)	315 (89%)	1332 (82%)	435 (81%)	468 (87%)	447 (83%)
Temperature (C)	N	151	209	357	353	1616	536	541	539
	<38 C	150 (99%)	205 (98%)	343 (96%)	346 (98%)	1593 (99%)	532 (99%)	522 (96%)	522 (97%)
	38 - 38.9 C	1 (1%)	4 (2%)	11 (3%)	7 (2%)	17 (1%)	4 (1%)	15 (3%)	12 (2%)
	39.0 - 39.9 C	0	0	3 (1%)	0	6 (<1%)	0	4 (1%)	5 (1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 15.2

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
INJECTION SITE					
Pain	N	307	105	838	464
	ANY	151 (49%)	45 (43%)	359 (43%)	231 (50%)
	MILD	114 (37%)	35 (33%)	266 (32%)	160 (34%)
	MODERATE	36 (12%)	10 (10%)	75 (9%)	57 (12%)
	SEVERE	1 (<1%)	0	18 (2%)	14 (3%)
Erythema (mm)	N	307	105	838	464
	ANY	66 (21%)	7 (7%)	126 (15%)	57 (12%)
	>0 - 25 mm	49 (16%)	6 (6%)	107 (13%)	45 (10%)
	>25 - 50 mm	7 (2%)	1 (1%)	9 (1%)	6 (1%)
	> 50 mm	10 (3%)	0	10 (1%)	6 (1%)
Induration (mm)	N	307	105	838	464
	ANY	46 (15%)	6 (6%)	104 (12%)	61 (13%)
	>0 - 25 mm	32 (10%)	6 (6%)	88 (11%)	48 (10%)
	>25 - 50 mm	8 (3%)	0	8 (1%)	6 (1%)
	> 50 mm	6 (2%)	0	8 (1%)	7 (2%)
SYSTEMIC					
Chills	N	307	105	838	464
	ANY	14 (5%)	7 (7%)	65 (8%)	39 (8%)
	MILD	11 (4%)	4 (4%)	40 (5%)	27 (6%)
	MODERATE	2 (1%)	3 (3%)	15 (2%)	9 (2%)
	SEVERE	1 (<1%)	0	10 (1%)	3 (1%)
Nausea	N	307	105	838	464
	ANY	28 (9%)	9 (9%)	69 (8%)	43 (9%)
	MILD	18 (6%)	5 (5%)	51 (6%)	30 (6%)
	MODERATE	7 (2%)	4 (4%)	13 (2%)	11 (2%)
	SEVERE	3 (1%)	0	5 (1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_19_34.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_19_34

Table 15.2

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
SYSTEMIC					
Malaise	N	307	105	838	464
	ANY	40 (13%)	15 (14%)	165 (20%)	104 (22%)
	MILD	25 (8%)	7 (7%)	106 (13%)	70 (15%)
	MODERATE	11 (4%)	5 (5%)	33 (4%)	30 (6%)
	SEVERE	4 (1%)	3 (3%)	26 (3%)	4 (1%)
Myalgia	N	307	105	838	464
	ANY	55 (18%)	21 (20%)	105 (13%)	63 (14%)
	MILD	40 (13%)	13 (12%)	66 (8%)	36 (8%)
	MODERATE	14 (5%)	6 (6%)	24 (3%)	24 (5%)
	SEVERE	1 (<1%)	2 (2%)	15 (2%)	3 (1%)
Arthralgia	N	307	105	838	464
	ANY	18 (6%)	6 (6%)	56 (7%)	36 (8%)
	MILD	14 (5%)	2 (2%)	38 (5%)	22 (5%)
	MODERATE	4 (1%)	3 (3%)	12 (1%)	13 (3%)
	SEVERE	0	1 (1%)	6 (1%)	1 (<1%)
Headache	N	307	105	838	464
	ANY	87 (28%)	23 (22%)	229 (27%)	135 (29%)
	MILD	55 (18%)	15 (14%)	148 (18%)	83 (18%)
	MODERATE	28 (9%)	5 (5%)	58 (7%)	40 (9%)
	SEVERE	4 (1%)	3 (3%)	23 (3%)	12 (3%)
Rash	N	307	105	838	464
	ANY	9 (3%)	0	30 (4%)	13 (3%)
	OTHER	4 (1%)	0	7 (1%)	4 (1%)
	URTICARIAL	5 (2%)	0	23 (3%)	9 (2%)
Fever (>= 38C)	N	307	105	838	464
	YES	4 (1%)	2 (2%)	27 (3%)	16 (3%)
	NO	303 (99%)	103 (98%)	811 (97%)	448 (97%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_19_34.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_19_34

Table 15.2

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	 P13 Menactra (N=105)	 P17 ACWY (N=838)	 P17 Menactra (N=464)
OTHER					
Stayed Home	N	297	103	836	463
	YES	7 (2%)	3 (3%)	40 (5%)	22 (5%)
	NO	290 (98%)	100 (97%)	796 (95%)	441 (95%)
Analgesic Antipyretics	N	307	105	838	464
	YES	64 (21%)	19 (18%)	144 (17%)	66 (14%)
	NO	243 (79%)	86 (82%)	694 (83%)	398 (86%)
Temperature (C)	N	307	105	838	464
	<38 C	303 (99%)	103 (98%)	811 (97%)	448 (97%)
	38 - 38.9 C	2 (1%)	1 (1%)	19 (2%)	13 (3%)
	39.0 - 39.9 C	2 (1%)	1 (1%)	6 (1%)	3 (1%)
	>= 40 C	0	0	2 (<1%)	0

Table 15.3

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
INJECTION SITE					
Pain	N	711	231	750	418
	ANY	240 (34%)	92 (40%)	273 (36%)	161 (39%)
	MILD	199 (28%)	81 (35%)	175 (23%)	108 (26%)
	MODERATE	39 (5%)	11 (5%)	75 (10%)	38 (9%)
	SEVERE	2 (<1%)	0	23 (3%)	15 (4%)
Erythema (mm)	N	711	231	750	418
	ANY	101 (14%)	34 (15%)	81 (11%)	48 (11%)
	>0 - 25 mm	72 (10%)	29 (13%)	66 (9%)	43 (10%)
	>25 - 50 mm	11 (2%)	2 (1%)	8 (1%)	4 (1%)
	> 50 mm	18 (3%)	3 (1%)	7 (1%)	1 (<1%)
Induration (mm)	N	711	231	750	418
	ANY	82 (12%)	23 (10%)	75 (10%)	54 (13%)
	>0 - 25 mm	60 (8%)	19 (8%)	66 (9%)	45 (11%)
	>25 - 50 mm	14 (2%)	3 (1%)	4 (1%)	6 (1%)
	> 50 mm	8 (1%)	1 (<1%)	5 (1%)	3 (1%)
SYSTEMIC					
Chills	N	711	231	750	418
	ANY	27 (4%)	5 (2%)	59 (8%)	31 (7%)
	MILD	20 (3%)	4 (2%)	32 (4%)	20 (5%)
	MODERATE	7 (1%)	1 (<1%)	18 (2%)	9 (2%)
	SEVERE	0	0	9 (1%)	2 (<1%)
Nausea	N	711	231	750	418
	ANY	45 (6%)	9 (4%)	43 (6%)	34 (8%)
	MILD	30 (4%)	7 (3%)	34 (5%)	25 (6%)
	MODERATE	14 (2%)	1 (<1%)	4 (1%)	7 (2%)
	SEVERE	1 (<1%)	1 (<1%)	5 (1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_35_55.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_35_55

Table 15.3

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
SYSTEMIC					
Malaise	N	711	231	750	418
	ANY	62 (9%)	19 (8%)	144 (19%)	82 (20%)
	MILD	35 (5%)	14 (6%)	84 (11%)	50 (12%)
	MODERATE	22 (3%)	3 (1%)	43 (6%)	24 (6%)
	SEVERE	5 (1%)	2 (1%)	17 (2%)	8 (2%)
Myalgia	N	711	231	750	418
	ANY	87 (12%)	29 (13%)	92 (12%)	68 (16%)
	MILD	60 (8%)	22 (10%)	48 (6%)	41 (10%)
	MODERATE	23 (3%)	4 (2%)	34 (5%)	20 (5%)
	SEVERE	4 (1%)	3 (1%)	10 (1%)	7 (2%)
Arthralgia	N	711	231	750	418
	ANY	42 (6%)	14 (6%)	62 (8%)	40 (10%)
	MILD	26 (4%)	11 (5%)	37 (5%)	22 (5%)
	MODERATE	12 (2%)	1 (<1%)	15 (2%)	12 (3%)
	SEVERE	4 (1%)	2 (1%)	10 (1%)	6 (1%)
Headache	N	711	231	750	418
	ANY	166 (23%)	61 (26%)	192 (26%)	119 (28%)
	MILD	108 (15%)	41 (18%)	123 (16%)	74 (18%)
	MODERATE	46 (6%)	18 (8%)	43 (6%)	31 (7%)
	SEVERE	12 (2%)	2 (1%)	26 (3%)	14 (3%)
Rash	N	711	231	750	418
	ANY	16 (2%)	2 (1%)	23 (3%)	9 (2%)
	OTHER	5 (1%)	2 (1%)	5 (1%)	1 (<1%)
	URTICARIAL	11 (2%)	0	18 (2%)	8 (2%)
Fever (>= 38C)	N	709	231	749	418
	YES	5 (1%)	0	29 (4%)	15 (4%)
	NO	704 (99%)	231 (100%)	720 (96%)	403 (96%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_35_55.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_35_55

Table 15.3

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	 P13 Menactra (N=231)	 P17 ACWY (N=750)	 P17 Menactra (N=418)
OTHER					
Stayed Home	N	709	230	749	417
	YES	10 (1%)	0	35 (5%)	24 (6%)
	NO	699 (99%)	230 (100%)	714 (95%)	393 (94%)
Analgesic Antipyretics	N	711	231	750	417
	YES	176 (25%)	55 (24%)	106 (14%)	82 (20%)
	NO	535 (75%)	176 (76%)	644 (86%)	335 (80%)
Temperature (C)	N	709	231	749	418
	<38 C	704 (99%)	231 (100%)	720 (96%)	403 (96%)
	38 - 38.9 C	4 (1%)	0	23 (3%)	9 (2%)
	39.0 - 39.9 C	1 (<1%)	0	4 (1%)	4 (1%)
	>= 40 C	0	0	2 (<1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONTROL_35_55.SAS(WARTERO) 10JUL08, 08:51 SAS.9.1 - PINJSUM_MEN_VS_CONTROL_35_55

Table 16

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
INJECTION SITE							
Pain	N	151	357	359	1623	541	540
	ANY	81 (54%)	116 (32%)	82 (23%)	714 (44%)	245 (45%)	263 (49%)
	MILD	67 (44%)	72 (20%)	52 (14%)	560 (35%)	162 (30%)	171 (32%)
	MODERATE	14 (9%)	34 (10%)	24 (7%)	138 (9%)	75 (14%)	76 (14%)
	SEVERE	0	10 (3%)	6 (2%)	16 (1%)	8 (1%)	16 (3%)
Erythema (mm)	N	151	357	359	1624	541	540
	ANY	57 (38%)	66 (18%)	48 (13%)	247 (15%)	66 (12%)	68 (13%)
	>0 - 25 mm	48 (32%)	58 (16%)	41 (11%)	180 (11%)	60 (11%)	59 (11%)
	>25 - 50 mm	4 (3%)	7 (2%)	6 (2%)	31 (2%)	3 (1%)	3 (1%)
	> 50 mm	5 (3%)	1 (<1%)	1 (<1%)	36 (2%)	3 (1%)	6 (1%)
Induration (mm)	N	151	357	359	1624	541	540
	ANY	34 (23%)	59 (17%)	41 (11%)	196 (12%)	70 (13%)	68 (13%)
	>0 - 25 mm	24 (16%)	45 (13%)	29 (8%)	135 (8%)	56 (10%)	50 (9%)
	>25 - 50 mm	4 (3%)	10 (3%)	11 (3%)	30 (2%)	8 (1%)	7 (1%)
	> 50 mm	6 (4%)	4 (1%)	1 (<1%)	31 (2%)	6 (1%)	11 (2%)
SYSTEMIC							
Chills	N	151	357	359	1625	541	540
	ANY	24 (16%)	47 (13%)	39 (11%)	127 (8%)	66 (12%)	77 (14%)
	MILD	17 (11%)	29 (8%)	29 (8%)	88 (5%)	42 (8%)	47 (9%)
	MODERATE	5 (3%)	12 (3%)	7 (2%)	30 (2%)	18 (3%)	23 (4%)
	SEVERE	2 (1%)	6 (2%)	3 (1%)	9 (1%)	6 (1%)	7 (1%)
Nausea	N	151	357	359	1625	541	540
	ANY	22 (15%)	28 (8%)	43 (12%)	187 (12%)	72 (13%)	88 (16%)
	MILD	15 (10%)	17 (5%)	33 (9%)	122 (8%)	45 (8%)	61 (11%)
	MODERATE	5 (3%)	7 (2%)	5 (1%)	55 (3%)	23 (4%)	19 (4%)
	SEVERE	2 (1%)	4 (1%)	5 (1%)	10 (1%)	4 (1%)	8 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_CONVAC_11_18

Table 16

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
SYSTEMIC							
Malaise	N	151	357	359	1625	541	540
	ANY	23 (15%)	43 (12%)	65 (18%)	177 (11%)	110 (20%)	132 (24%)
	MILD	13 (9%)	23 (6%)	35 (10%)	105 (6%)	71 (13%)	79 (15%)
	MODERATE	7 (5%)	15 (4%)	21 (6%)	56 (3%)	32 (6%)	38 (7%)
	SEVERE	3 (2%)	5 (1%)	9 (3%)	16 (1%)	7 (1%)	15 (3%)
Myalgia	N	151	357	359	1625	541	540
	ANY	35 (23%)	79 (22%)	118 (33%)	310 (19%)	104 (19%)	145 (27%)
	MILD	28 (19%)	46 (13%)	58 (16%)	223 (14%)	67 (12%)	97 (18%)
	MODERATE	6 (4%)	24 (7%)	44 (12%)	63 (4%)	30 (6%)	31 (6%)
	SEVERE	1 (1%)	9 (3%)	16 (4%)	24 (1%)	7 (1%)	17 (3%)
Arthralgia	N	151	357	359	1625	541	540
	ANY	12 (8%)	40 (11%)	57 (16%)	137 (8%)	62 (11%)	94 (17%)
	MILD	12 (8%)	24 (7%)	28 (8%)	102 (6%)	40 (7%)	60 (11%)
	MODERATE	0	7 (2%)	19 (5%)	28 (2%)	19 (4%)	22 (4%)
	SEVERE	0	9 (3%)	10 (3%)	7 (<1%)	3 (1%)	12 (2%)
Headache	N	151	357	359	1625	541	540
	ANY	62 (41%)	128 (36%)	129 (36%)	478 (29%)	194 (36%)	216 (40%)
	MILD	42 (28%)	82 (23%)	70 (19%)	322 (20%)	101 (19%)	131 (24%)
	MODERATE	13 (9%)	27 (8%)	34 (9%)	123 (8%)	70 (13%)	54 (10%)
	SEVERE	7 (5%)	19 (5%)	25 (7%)	33 (2%)	23 (4%)	31 (6%)
Rash	N	0	0	0	1625	541	540
	ANY	0	0	0	44 (3%)	17 (3%)	21 (4%)
	OTHER	0	0	0	21 (1%)	1 (<1%)	0
	URTICARIAL	0	0	0	23 (1%)	16 (3%)	21 (4%)
Fever (>= 38C)	N	151	357	359	1616	541	540
	YES	1 (1%)	14 (4%)	11 (3%)	23 (1%)	19 (4%)	28 (5%)
	NO	150 (99%)	343 (96%)	348 (97%)	1593 (99%)	522 (96%)	512 (95%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_CONVAC_11_18

Table 16

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
OTHER							
Stayed Home	N	150	357	358	1611	509	513
	YES	6 (4%)	12 (3%)	12 (3%)	52 (3%)	40 (8%)	54 (11%)
	NO	144 (96%)	345 (97%)	346 (97%)	1559 (97%)	469 (92%)	459 (89%)
Analgesic Antipyretics	N	151	357	359	1625	541	540
	YES	39 (26%)	31 (9%)	38 (11%)	293 (18%)	73 (13%)	102 (19%)
	NO	112 (74%)	326 (91%)	321 (89%)	1332 (82%)	468 (87%)	438 (81%)
Temperature (C)	N	151	357	359	1616	541	540
	<38 C	150 (99%)	343 (96%)	348 (97%)	1593 (99%)	522 (96%)	512 (95%)
	38 - 38.9 C	1 (1%)	11 (3%)	9 (3%)	17 (1%)	15 (3%)	24 (4%)
	39.0 - 39.9 C	0	3 (1%)	2 (1%)	6 (<1%)	4 (1%)	2 (<1%)
	>= 40 C	0	0	0	0	0	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_CONVAC_11_18

Table 17

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
INJECTION SITE						
Pain	N	151	357	1623	541	503
	ANY	81 (54%)	116 (32%)	714 (44%)	245 (45%)	239 (48%)
	MILD	67 (44%)	72 (20%)	560 (35%)	162 (30%)	153 (30%)
	MODERATE	14 (9%)	34 (10%)	138 (9%)	75 (14%)	70 (14%)
	SEVERE	0	10 (3%)	16 (1%)	8 (1%)	16 (3%)
Erythema (mm)	N	151	357	1624	541	503
	ANY	57 (38%)	66 (18%)	247 (15%)	66 (12%)	64 (13%)
	>0 - 25 mm	48 (32%)	58 (16%)	180 (11%)	60 (11%)	56 (11%)
	>25 - 50 mm	4 (3%)	7 (2%)	31 (2%)	3 (1%)	2 (<1%)
	> 50 mm	5 (3%)	1 (<1%)	36 (2%)	3 (1%)	6 (1%)
Induration (mm)	N	151	357	1624	541	503
	ANY	34 (23%)	59 (17%)	196 (12%)	70 (13%)	64 (13%)
	>0 - 25 mm	24 (16%)	45 (13%)	135 (8%)	56 (10%)	53 (11%)
	>25 - 50 mm	4 (3%)	10 (3%)	30 (2%)	8 (1%)	6 (1%)
	> 50 mm	6 (4%)	4 (1%)	31 (2%)	6 (1%)	5 (1%)
SYSTEMIC						
Chills	N	151	357	1625	541	503
	ANY	24 (16%)	47 (13%)	127 (8%)	66 (12%)	45 (9%)
	MILD	17 (11%)	29 (8%)	88 (5%)	42 (8%)	32 (6%)
	MODERATE	5 (3%)	12 (3%)	30 (2%)	18 (3%)	7 (1%)
	SEVERE	2 (1%)	6 (2%)	9 (1%)	6 (1%)	6 (1%)
Nausea	N	151	357	1625	541	503
	ANY	22 (15%)	28 (8%)	187 (12%)	72 (13%)	64 (13%)
	MILD	15 (10%)	17 (5%)	122 (8%)	45 (8%)	47 (9%)
	MODERATE	5 (3%)	7 (2%)	55 (3%)	23 (4%)	12 (2%)
	SEVERE	2 (1%)	4 (1%)	10 (1%)	4 (1%)	5 (1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_TDAP_11_18.SAS(WARTER0) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_TDAP_11_18

Table 17

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Malaise	N	151	357	1625	541	503
	ANY	23 (15%)	43 (12%)	177 (11%)	110 (20%)	87 (17%)
	MILD	13 (9%)	23 (6%)	105 (6%)	71 (13%)	52 (10%)
	MODERATE	7 (5%)	15 (4%)	56 (3%)	32 (6%)	21 (4%)
	SEVERE	3 (2%)	5 (1%)	16 (1%)	7 (1%)	14 (3%)
Myalgia	N	151	357	1625	541	503
	ANY	35 (23%)	79 (22%)	310 (19%)	104 (19%)	82 (16%)
	MILD	28 (19%)	46 (13%)	223 (14%)	67 (12%)	50 (10%)
	MODERATE	6 (4%)	24 (7%)	63 (4%)	30 (6%)	24 (5%)
	SEVERE	1 (1%)	9 (3%)	24 (1%)	7 (1%)	8 (2%)
Arthralgia	N	151	357	1625	541	503
	ANY	12 (8%)	40 (11%)	137 (8%)	62 (11%)	52 (10%)
	MILD	12 (8%)	24 (7%)	102 (6%)	40 (7%)	36 (7%)
	MODERATE	0	7 (2%)	28 (2%)	19 (4%)	15 (3%)
	SEVERE	0	9 (3%)	7 (<1%)	3 (1%)	1 (<1%)
Headache	N	151	357	1625	541	503
	ANY	62 (41%)	128 (36%)	478 (29%)	194 (36%)	138 (27%)
	MILD	42 (28%)	82 (23%)	322 (20%)	101 (19%)	71 (14%)
	MODERATE	13 (9%)	27 (8%)	123 (8%)	70 (13%)	49 (10%)
	SEVERE	7 (5%)	19 (5%)	33 (2%)	23 (4%)	18 (4%)
Rash	N	0	0	1625	541	503
	ANY	0	0	44 (3%)	17 (3%)	13 (3%)
	OTHER	0	0	21 (1%)	1 (<1%)	1 (<1%)
	URTICARIAL	0	0	23 (1%)	16 (3%)	12 (2%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_TDAP_11_18.SAS(WARTER0) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_TDAP_11_18

Table 17

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Fever (>= 38C)	N	151	357	1616	541	503
	YES	1 (1%)	14 (4%)	23 (1%)	19 (4%)	30 (6%)
	NO	150 (99%)	343 (96%)	1593 (99%)	522 (96%)	473 (94%)
OTHER						
Stayed Home	N	150	357	1611	509	486
	YES	6 (4%)	12 (3%)	52 (3%)	40 (8%)	25 (5%)
	NO	144 (96%)	345 (97%)	1559 (97%)	469 (92%)	461 (95%)
Analgesic Antipyretics	N	151	357	1625	541	503
	YES	39 (26%)	31 (9%)	293 (18%)	73 (13%)	51 (10%)
	NO	112 (74%)	326 (91%)	1332 (82%)	468 (87%)	452 (90%)
Temperature (C)	N	151	357	1616	541	503
	<38 C	150 (99%)	343 (96%)	1593 (99%)	522 (96%)	473 (94%)
	38 - 38.9 C	1 (1%)	11 (3%)	17 (1%)	15 (3%)	24 (5%)
	39.0 - 39.9 C	0	3 (1%)	6 (<1%)	4 (1%)	6 (1%)
	>= 40 C	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:52 SAS.9.1 - PINJSUM_MEN_VS_TDAP_11_18

Table 18

Summary of Reactogenicity on Days 1 to 3, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
INJECTION SITE						
Pain	N	3571	1145	1461	6177	1757
	ANY	1463 (41%)	497 (43%)	489 (33%)	2449 (40%)	806 (46%)
	MILD	1066 (30%)	372 (32%)	371 (25%)	1809 (29%)	605 (34%)
	MODERATE	344 (10%)	109 (10%)	99 (7%)	552 (9%)	169 (10%)
	SEVERE	53 (1%)	16 (1%)	19 (1%)	88 (1%)	32 (2%)
Erythema (mm)	N	3572	1145	1461	6178	1757
	ANY	530 (15%)	177 (15%)	168 (11%)	875 (14%)	224 (13%)
	>0 - 25 mm	435 (12%)	149 (13%)	138 (9%)	722 (12%)	188 (11%)
	>25 - 50 mm	52 (1%)	18 (2%)	17 (1%)	87 (1%)	22 (1%)
	> 50 mm	43 (1%)	10 (1%)	13 (1%)	66 (1%)	14 (1%)
Induration (mm)	N	3572	1145	1461	6178	1757
	ANY	447 (13%)	140 (12%)	144 (10%)	731 (12%)	200 (11%)
	>0 - 25 mm	329 (9%)	116 (10%)	118 (8%)	563 (9%)	164 (9%)
	>25 - 50 mm	67 (2%)	16 (1%)	17 (1%)	100 (2%)	25 (1%)
	> 50 mm	51 (1%)	8 (1%)	9 (1%)	68 (1%)	11 (1%)
SYSTEMIC						
Chills	N	3573	1145	1461	6179	1757
	ANY	306 (9%)	64 (6%)	61 (4%)	431 (7%)	88 (5%)
	MILD	210 (6%)	42 (4%)	39 (3%)	291 (5%)	62 (4%)
	MODERATE	71 (2%)	13 (1%)	17 (1%)	101 (2%)	22 (1%)
	SEVERE	25 (1%)	9 (1%)	5 (<1%)	39 (1%)	4 (<1%)
Nausea	N	3573	1145	1461	6179	1757
	ANY	344 (10%)	72 (6%)	68 (5%)	484 (8%)	106 (6%)
	MILD	237 (7%)	55 (5%)	52 (4%)	344 (6%)	80 (5%)
	MODERATE	85 (2%)	13 (1%)	15 (1%)	113 (2%)	23 (1%)
	SEVERE	22 (1%)	4 (<1%)	1 (<1%)	27 (<1%)	3 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D13.SAS(WARTERO) 10JUL08, 08:44 SAS.9.1 - PINJSUM_ACWY_D13

Table 18

Summary of Reactogenicity on Days 1 to 3, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Malaise	N	3573	1145	1461	6179	1757
	ANY	480 (13%)	175 (15%)	160 (11%)	815 (13%)	235 (13%)
	MILD	300 (8%)	117 (10%)	101 (7%)	518 (8%)	154 (9%)
	MODERATE	136 (4%)	36 (3%)	48 (3%)	220 (4%)	69 (4%)
	SEVERE	44 (1%)	22 (2%)	11 (1%)	77 (1%)	12 (1%)
Myalgia	N	3573	1145	1461	6179	1757
	ANY	730 (20%)	146 (13%)	138 (9%)	1014 (16%)	226 (13%)
	MILD	489 (14%)	101 (9%)	85 (6%)	675 (11%)	153 (9%)
	MODERATE	178 (5%)	31 (3%)	43 (3%)	252 (4%)	63 (4%)
	SEVERE	63 (2%)	14 (1%)	10 (1%)	87 (1%)	10 (1%)
Arthralgia	N	3573	1145	1461	6179	1757
	ANY	341 (10%)	64 (6%)	80 (5%)	485 (8%)	99 (6%)
	MILD	226 (6%)	46 (4%)	55 (4%)	327 (5%)	67 (4%)
	MODERATE	80 (2%)	12 (1%)	15 (1%)	107 (2%)	27 (2%)
	SEVERE	35 (1%)	6 (1%)	10 (1%)	51 (1%)	5 (<1%)
Headache	N	3573	1145	1461	6179	1757
	ANY	1003 (28%)	262 (23%)	285 (20%)	1550 (25%)	392 (22%)
	MILD	667 (19%)	178 (16%)	196 (13%)	1041 (17%)	273 (16%)
	MODERATE	238 (7%)	65 (6%)	69 (5%)	372 (6%)	93 (5%)
	SEVERE	98 (3%)	19 (2%)	20 (1%)	137 (2%)	26 (1%)
Rash	N	2706	1145	1461	5312	1757
	ANY	53 (2%)	27 (2%)	26 (2%)	106 (2%)	32 (2%)
	OTHER	14 (1%)	11 (1%)	9 (1%)	34 (1%)	11 (1%)
	URTICARIAL	39 (1%)	16 (1%)	17 (1%)	72 (1%)	21 (1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D13.SAS(WARTER0) 10JUL08, 08:44 SAS.9.1 - PINJSUM_ACWY_D13

Table 18

Summary of Reactogenicity on Days 1 to 3, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Fever (>= 38C)	N	3564	1145	1458	6167	1754
	YES	71 (2%)	23 (2%)	21 (1%)	115 (2%)	26 (1%)
	NO	3493 (98%)	1122 (98%)	1437 (99%)	6052 (98%)	1728 (99%)
OTHER						
Stayed Home	N	3498	1133	1457	6088	1745
	YES	150 (4%)	41 (4%)	37 (3%)	228 (4%)	43 (2%)
	NO	3348 (96%)	1092 (96%)	1420 (97%)	5860 (96%)	1702 (98%)
Analgesic Antipyretics	N	3573	1145	1461	6179	1756
	YES	439 (12%)	160 (14%)	216 (15%)	815 (13%)	254 (14%)
	NO	3134 (88%)	985 (86%)	1245 (85%)	5364 (87%)	1502 (86%)
Temperature (C)	N	3564	1145	1458	6167	1754
	<38 C	3493 (98%)	1122 (98%)	1437 (99%)	6052 (98%)	1728 (99%)
	38 - 38.9 C	64 (2%)	15 (1%)	16 (1%)	95 (2%)	19 (1%)
	39.0 - 39.9 C	7 (<1%)	6 (1%)	4 (<1%)	17 (<1%)	5 (<1%)
	>= 40 C	0	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D13.SAS(WARTERO) 10JUL08, 08:44 SAS.9.1 - PINJSUM_ACWY_D13

Table 19.1

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
INJECTION SITE									
Pain	N	151	209	357	353	1623	539	541	539
	ANY	81 (54%)	112 (54%)	114 (32%)	246 (70%)	697 (43%)	285 (53%)	234 (43%)	376 (70%)
	MILD	67 (44%)	89 (43%)	72 (20%)	135 (38%)	550 (34%)	219 (41%)	158 (29%)	218 (40%)
	MODERATE	14 (9%)	21 (10%)	32 (9%)	94 (27%)	133 (8%)	59 (11%)	69 (13%)	134 (25%)
	SEVERE	0	2 (1%)	10 (3%)	17 (5%)	14 (1%)	7 (1%)	7 (1%)	24 (4%)
Erythema (mm)	N	151	209	357	353	1624	539	541	539
	ANY	57 (38%)	39 (19%)	66 (18%)	102 (29%)	235 (14%)	84 (16%)	61 (11%)	66 (12%)
	>0 - 25 mm	48 (32%)	38 (18%)	60 (17%)	86 (24%)	173 (11%)	69 (13%)	56 (10%)	61 (11%)
	>25 - 50 mm	4 (3%)	1 (<1%)	6 (2%)	13 (4%)	30 (2%)	9 (2%)	3 (1%)	4 (1%)
	> 50 mm	5 (3%)	0	0	3 (1%)	32 (2%)	6 (1%)	2 (<1%)	1 (<1%)
Induration (mm)	N	151	209	357	353	1624	539	541	539
	ANY	34 (23%)	23 (11%)	58 (16%)	117 (33%)	191 (12%)	59 (11%)	64 (12%)	105 (19%)
	>0 - 25 mm	25 (17%)	22 (11%)	46 (13%)	80 (23%)	132 (8%)	47 (9%)	52 (10%)	76 (14%)
	>25 - 50 mm	3 (2%)	0	9 (3%)	31 (9%)	32 (2%)	8 (1%)	6 (1%)	20 (4%)
	> 50 mm	6 (4%)	1 (<1%)	3 (1%)	6 (2%)	27 (2%)	4 (1%)	6 (1%)	9 (2%)
SYSTEMIC									
Chills	N	151	209	357	353	1625	539	541	539
	ANY	16 (11%)	13 (6%)	34 (10%)	37 (10%)	107 (7%)	29 (5%)	52 (10%)	54 (10%)
	MILD	11 (7%)	12 (6%)	22 (6%)	28 (8%)	78 (5%)	21 (4%)	35 (6%)	40 (7%)
	MODERATE	3 (2%)	1 (<1%)	8 (2%)	6 (2%)	23 (1%)	8 (1%)	13 (2%)	12 (2%)
	SEVERE	2 (1%)	0	4 (1%)	3 (1%)	6 (<1%)	0	4 (1%)	2 (<1%)
Nausea	N	151	209	357	353	1625	539	541	539
	ANY	16 (11%)	11 (5%)	20 (6%)	28 (8%)	143 (9%)	40 (7%)	57 (11%)	66 (12%)
	MILD	12 (8%)	7 (3%)	13 (4%)	20 (6%)	99 (6%)	29 (5%)	36 (7%)	46 (9%)
	MODERATE	3 (2%)	3 (1%)	5 (1%)	6 (2%)	37 (2%)	10 (2%)	19 (4%)	18 (3%)
	SEVERE	1 (1%)	1 (<1%)	2 (1%)	2 (1%)	7 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_11_18_D13.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MEN_CONT_11_18_D13

Table 19.1

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
SYSTEMIC									
Malaise	N	151	209	357	353	1625	539	541	539
	ANY	15 (10%)	14 (7%)	37 (10%)	47 (13%)	147 (9%)	58 (11%)	99 (18%)	99 (18%)
	MILD	9 (6%)	10 (5%)	21 (6%)	33 (9%)	91 (6%)	33 (6%)	69 (13%)	62 (12%)
	MODERATE	3 (2%)	4 (2%)	13 (4%)	9 (3%)	44 (3%)	23 (4%)	24 (4%)	31 (6%)
	SEVERE	3 (2%)	0	3 (1%)	5 (1%)	12 (1%)	2 (<1%)	6 (1%)	6 (1%)
Myalgia	N	151	209	357	353	1625	539	541	539
	ANY	30 (20%)	20 (10%)	74 (21%)	124 (35%)	276 (17%)	84 (16%)	95 (18%)	131 (24%)
	MILD	24 (16%)	15 (7%)	48 (13%)	79 (22%)	201 (12%)	60 (11%)	64 (12%)	83 (15%)
	MODERATE	5 (3%)	5 (2%)	20 (6%)	37 (10%)	56 (3%)	22 (4%)	25 (5%)	38 (7%)
	SEVERE	1 (1%)	0	6 (2%)	8 (2%)	19 (1%)	2 (<1%)	6 (1%)	10 (2%)
Arthralgia	N	151	209	357	353	1625	539	541	539
	ANY	7 (5%)	4 (2%)	34 (10%)	57 (16%)	107 (7%)	26 (5%)	51 (9%)	68 (13%)
	MILD	7 (5%)	3 (1%)	20 (6%)	33 (9%)	82 (5%)	23 (4%)	35 (6%)	44 (8%)
	MODERATE	0	1 (<1%)	7 (2%)	20 (6%)	19 (1%)	3 (1%)	14 (3%)	19 (4%)
	SEVERE	0	0	7 (2%)	4 (1%)	6 (<1%)	0	2 (<1%)	5 (1%)
Headache	N	151	209	357	353	1625	539	541	539
	ANY	47 (31%)	63 (30%)	106 (30%)	94 (27%)	372 (23%)	124 (23%)	172 (32%)	173 (32%)
	MILD	35 (23%)	45 (22%)	72 (20%)	68 (19%)	267 (16%)	92 (17%)	99 (18%)	109 (20%)
	MODERATE	8 (5%)	15 (7%)	21 (6%)	16 (5%)	87 (5%)	27 (5%)	53 (10%)	45 (8%)
	SEVERE	4 (3%)	3 (1%)	13 (4%)	10 (3%)	18 (1%)	5 (1%)	20 (4%)	19 (4%)
Rash	N	0	0	0	0	1625	539	541	539
	ANY	0	0	0	0	28 (2%)	14 (3%)	11 (2%)	15 (3%)
	OTHER	0	0	0	0	13 (1%)	5 (1%)	1 (<1%)	2 (<1%)
	URTICARIAL	0	0	0	0	15 (1%)	9 (2%)	10 (2%)	13 (2%)
Fever (>= 38C)	N	151	209	357	353	1616	536	541	539
	YES	0	0	8 (2%)	7 (2%)	18 (1%)	3 (1%)	14 (3%)	12 (2%)
	NO	151 (100%)	209 (100%)	349 (98%)	346 (98%)	1598 (99%)	533 (99%)	527 (97%)	527 (98%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_11_18_D13.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MEN_CONT_11_18_D13

Table 19.1

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
OTHER									
Stayed Home	N	150	209	357	353	1611	532	509	502
	YES	5 (3%)	2 (1%)	8 (2%)	14 (4%)	38 (2%)	11 (2%)	38 (7%)	37 (7%)
	NO	145 (97%)	207 (99%)	349 (98%)	339 (96%)	1573 (98%)	521 (98%)	471 (93%)	465 (93%)
Analgesic Antipyretics	N	151	209	357	353	1625	539	541	539
	YES	27 (18%)	36 (17%)	19 (5%)	35 (10%)	221 (14%)	81 (15%)	56 (10%)	75 (14%)
	NO	124 (82%)	173 (83%)	338 (95%)	318 (90%)	1404 (86%)	458 (85%)	485 (90%)	464 (86%)
Temperature (C)	N	151	209	357	353	1616	536	541	539
	<38 C	151 (100%)	209 (100%)	349 (98%)	346 (98%)	1598 (99%)	533 (99%)	527 (97%)	527 (98%)
	38 - 38.9 C	0	0	7 (2%)	7 (2%)	15 (1%)	3 (1%)	13 (2%)	8 (1%)
	39.0 - 39.9 C	0	0	1 (<1%)	0	3 (<1%)	0	1 (<1%)	4 (1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 19.2

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
INJECTION SITE					
Pain	N	307	105	838	464
	ANY	145 (47%)	45 (43%)	352 (42%)	229 (49%)
	MILD	109 (36%)	36 (34%)	263 (31%)	160 (34%)
	MODERATE	35 (11%)	9 (9%)	74 (9%)	55 (12%)
	SEVERE	1 (<1%)	0	15 (2%)	14 (3%)
Erythema (mm)	N	307	105	838	464
	ANY	60 (20%)	6 (6%)	117 (14%)	56 (12%)
	>0 - 25 mm	46 (15%)	6 (6%)	103 (12%)	44 (9%)
	>25 - 50 mm	10 (3%)	0	8 (1%)	6 (1%)
	> 50 mm	4 (1%)	0	6 (1%)	6 (1%)
Induration (mm)	N	307	105	838	464
	ANY	42 (14%)	6 (6%)	98 (12%)	59 (13%)
	>0 - 25 mm	30 (10%)	6 (6%)	86 (10%)	46 (10%)
	>25 - 50 mm	11 (4%)	0	5 (1%)	8 (2%)
	> 50 mm	1 (<1%)	0	7 (1%)	5 (1%)
SYSTEMIC					
Chills	N	307	105	838	464
	ANY	12 (4%)	4 (4%)	52 (6%)	29 (6%)
	MILD	11 (4%)	2 (2%)	31 (4%)	21 (5%)
	MODERATE	0	2 (2%)	13 (2%)	6 (1%)
	SEVERE	1 (<1%)	0	8 (1%)	2 (<1%)
Nausea	N	307	105	838	464
	ANY	22 (7%)	4 (4%)	50 (6%)	32 (7%)
	MILD	15 (5%)	2 (2%)	40 (5%)	25 (5%)
	MODERATE	6 (2%)	2 (2%)	7 (1%)	7 (2%)
	SEVERE	1 (<1%)	0	3 (<1%)	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D13.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D13

Table 19.2

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
SYSTEMIC					
Malaise	N	307	105	838	464
	ANY	33 (11%)	9 (9%)	142 (17%)	85 (18%)
	MILD	21 (7%)	5 (5%)	96 (11%)	61 (13%)
	MODERATE	9 (3%)	3 (3%)	27 (3%)	22 (5%)
	SEVERE	3 (1%)	1 (1%)	19 (2%)	2 (<1%)
Myalgia	N	307	105	838	464
	ANY	52 (17%)	16 (15%)	94 (11%)	51 (11%)
	MILD	38 (12%)	12 (11%)	63 (8%)	30 (6%)
	MODERATE	13 (4%)	3 (3%)	18 (2%)	19 (4%)
	SEVERE	1 (<1%)	1 (1%)	13 (2%)	2 (<1%)
Arthralgia	N	307	105	838	464
	ANY	16 (5%)	4 (4%)	48 (6%)	27 (6%)
	MILD	12 (4%)	2 (2%)	34 (4%)	18 (4%)
	MODERATE	4 (1%)	2 (2%)	8 (1%)	8 (2%)
	SEVERE	0	0	6 (1%)	1 (<1%)
Headache	N	307	105	838	464
	ANY	69 (22%)	18 (17%)	193 (23%)	111 (24%)
	MILD	48 (16%)	11 (10%)	130 (16%)	72 (16%)
	MODERATE	20 (7%)	4 (4%)	45 (5%)	29 (6%)
	SEVERE	1 (<1%)	3 (3%)	18 (2%)	10 (2%)
Rash	N	307	105	838	464
	ANY	7 (2%)	0	20 (2%)	11 (2%)
	OTHER	3 (1%)	0	8 (1%)	3 (1%)
	URTICARIAL	4 (1%)	0	12 (1%)	8 (2%)
Fever (>= 38C)	N	307	105	838	464
	YES	2 (1%)	1 (1%)	21 (3%)	11 (2%)
	NO	305 (99%)	104 (99%)	817 (97%)	453 (98%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D13.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D13

Table 19.2

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
OTHER					
Stayed Home	N	297	103	836	463
	YES	7 (2%)	1 (1%)	34 (4%)	14 (3%)
	NO	290 (98%)	102 (99%)	802 (96%)	449 (97%)
Analgesic Antipyretics	N	307	105	838	464
	YES	50 (16%)	14 (13%)	110 (13%)	49 (11%)
	NO	257 (84%)	91 (87%)	728 (87%)	415 (89%)
Temperature (C)	N	307	105	838	464
	<38 C	305 (99%)	104 (99%)	817 (97%)	453 (98%)
	38 - 38.9 C	1 (<1%)	0	14 (2%)	10 (2%)
	39.0 - 39.9 C	1 (<1%)	1 (1%)	5 (1%)	1 (<1%)
	>= 40 C	0	0	2 (<1%)	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D13.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D13

Table 19.3

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
INJECTION SITE					
Pain	N	711	231	750	418
	ANY	231 (32%)	90 (39%)	258 (34%)	157 (38%)
	MILD	199 (28%)	80 (35%)	172 (23%)	110 (26%)
	MODERATE	32 (5%)	10 (4%)	67 (9%)	36 (9%)
	SEVERE	0	0	19 (3%)	11 (3%)
Erythema (mm)	N	711	231	750	418
	ANY	95 (13%)	33 (14%)	73 (10%)	45 (11%)
	>0 - 25 mm	76 (11%)	28 (12%)	62 (8%)	41 (10%)
	>25 - 50 mm	11 (2%)	3 (1%)	6 (1%)	4 (1%)
	> 50 mm	8 (1%)	2 (1%)	5 (1%)	0
Induration (mm)	N	711	231	750	418
	ANY	78 (11%)	22 (10%)	66 (9%)	54 (13%)
	>0 - 25 mm	59 (8%)	18 (8%)	59 (8%)	47 (11%)
	>25 - 50 mm	13 (2%)	3 (1%)	4 (1%)	6 (1%)
	> 50 mm	6 (1%)	1 (<1%)	3 (<1%)	1 (<1%)
SYSTEMIC					
Chills	N	711	231	750	418
	ANY	20 (3%)	4 (2%)	41 (5%)	22 (5%)
	MILD	15 (2%)	4 (2%)	24 (3%)	14 (3%)
	MODERATE	5 (1%)	0	12 (2%)	6 (1%)
	SEVERE	0	0	5 (1%)	2 (<1%)
Nausea	N	711	231	750	418
	ANY	39 (5%)	6 (3%)	29 (4%)	24 (6%)
	MILD	27 (4%)	5 (2%)	25 (3%)	19 (5%)
	MODERATE	12 (2%)	0	3 (<1%)	4 (1%)
	SEVERE	0	1 (<1%)	1 (<1%)	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_35_55_D13.SAS(WARTERO) 10JUL08, 09:36 SAS.9.1 - PINJSUM_MEN_CONT_35_55_D13

Table 19.3

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
SYSTEMIC					
Malaise	N	711	231	750	418
	ANY	47 (7%)	14 (6%)	113 (15%)	69 (17%)
	MILD	30 (4%)	11 (5%)	71 (9%)	44 (11%)
	MODERATE	15 (2%)	2 (1%)	33 (4%)	19 (5%)
	SEVERE	2 (<1%)	1 (<1%)	9 (1%)	6 (1%)
Myalgia	N	711	231	750	418
	ANY	66 (9%)	23 (10%)	72 (10%)	52 (12%)
	MILD	46 (6%)	17 (7%)	39 (5%)	34 (8%)
	MODERATE	18 (3%)	4 (2%)	25 (3%)	15 (4%)
	SEVERE	2 (<1%)	2 (1%)	8 (1%)	3 (1%)
Arthralgia	N	711	231	750	418
	ANY	32 (5%)	13 (6%)	48 (6%)	29 (7%)
	MILD	23 (3%)	10 (4%)	32 (4%)	14 (3%)
	MODERATE	7 (1%)	2 (1%)	8 (1%)	12 (3%)
	SEVERE	2 (<1%)	1 (<1%)	8 (1%)	3 (1%)
Headache	N	711	231	750	418
	ANY	130 (18%)	44 (19%)	155 (21%)	95 (23%)
	MILD	87 (12%)	34 (15%)	109 (15%)	64 (15%)
	MODERATE	37 (5%)	9 (4%)	32 (4%)	24 (6%)
	SEVERE	6 (1%)	1 (<1%)	14 (2%)	7 (2%)
Rash	N	711	231	750	418
	ANY	11 (2%)	1 (<1%)	15 (2%)	6 (1%)
	OTHER	5 (1%)	1 (<1%)	4 (1%)	2 (<1%)
	URTICARIAL	6 (1%)	0	11 (1%)	4 (1%)
Fever (>= 38C)	N	709	231	749	418
	YES	3 (<1%)	0	18 (2%)	11 (3%)
	NO	706 (100%)	231 (100%)	731 (98%)	407 (97%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_35_55_D13.SAS(WARTERO) 10JUL08, 09:36 SAS.9.1 - PINJSUM_MEN_CONT_35_55_D13

Table 19.3

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
OTHER					
Stayed Home	N	709	230	748	417
	YES	8 (1%)	0	29 (4%)	17 (4%)
	NO	701 (99%)	230 (100%)	719 (96%)	400 (96%)
Analgesic Antipyretics	N	711	231	750	417
	YES	134 (19%)	42 (18%)	82 (11%)	68 (16%)
	NO	577 (81%)	189 (82%)	668 (89%)	349 (84%)
Temperature (C)	N	709	231	749	418
	<38 C	706 (100%)	231 (100%)	731 (98%)	407 (97%)
	38 - 38.9 C	2 (<1%)	0	14 (2%)	6 (1%)
	39.0 - 39.9 C	1 (<1%)	0	3 (<1%)	3 (1%)
	>= 40 C	0	0	1 (<1%)	2 (<1%)

Table 20

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
INJECTION SITE							
Pain	N	151	357	359	1623	541	540
	ANY	81 (54%)	114 (32%)	80 (22%)	697 (43%)	234 (43%)	257 (48%)
	MILD	67 (44%)	72 (20%)	50 (14%)	550 (34%)	158 (29%)	169 (31%)
	MODERATE	14 (9%)	32 (9%)	24 (7%)	133 (8%)	69 (13%)	72 (13%)
	SEVERE	0	10 (3%)	6 (2%)	14 (1%)	7 (1%)	16 (3%)
Erythema (mm)	N	151	357	359	1624	541	540
	ANY	57 (38%)	66 (18%)	46 (13%)	235 (14%)	61 (11%)	65 (12%)
	>0 - 25 mm	48 (32%)	60 (17%)	41 (11%)	173 (11%)	56 (10%)	57 (11%)
	>25 - 50 mm	4 (3%)	6 (2%)	5 (1%)	30 (2%)	3 (1%)	4 (1%)
	> 50 mm	5 (3%)	0	0	32 (2%)	2 (<1%)	4 (1%)
Induration (mm)	N	151	357	359	1624	541	540
	ANY	34 (23%)	58 (16%)	37 (10%)	191 (12%)	64 (12%)	63 (12%)
	>0 - 25 mm	25 (17%)	46 (13%)	27 (8%)	132 (8%)	52 (10%)	47 (9%)
	>25 - 50 mm	3 (2%)	9 (3%)	10 (3%)	32 (2%)	6 (1%)	7 (1%)
	> 50 mm	6 (4%)	3 (1%)	0	27 (2%)	6 (1%)	9 (2%)
SYSTEMIC							
Chills	N	151	357	359	1625	541	540
	ANY	16 (11%)	34 (10%)	33 (9%)	107 (7%)	52 (10%)	64 (12%)
	MILD	11 (7%)	22 (6%)	25 (7%)	78 (5%)	35 (6%)	39 (7%)
	MODERATE	3 (2%)	8 (2%)	5 (1%)	23 (1%)	13 (2%)	19 (4%)
	SEVERE	2 (1%)	4 (1%)	3 (1%)	6 (<1%)	4 (1%)	6 (1%)
Nausea	N	151	357	359	1625	541	540
	ANY	16 (11%)	20 (6%)	36 (10%)	143 (9%)	57 (11%)	72 (13%)
	MILD	12 (8%)	13 (4%)	28 (8%)	99 (6%)	36 (7%)	49 (9%)
	MODERATE	3 (2%)	5 (1%)	4 (1%)	37 (2%)	19 (4%)	17 (3%)
	SEVERE	1 (1%)	2 (1%)	4 (1%)	7 (<1%)	2 (<1%)	6 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D13

Table 20

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
SYSTEMIC							
Malaise	N	151	357	359	1625	541	540
	ANY	15 (10%)	37 (10%)	60 (17%)	147 (9%)	99 (18%)	122 (23%)
	MILD	9 (6%)	21 (6%)	33 (9%)	91 (6%)	69 (13%)	77 (14%)
	MODERATE	3 (2%)	13 (4%)	18 (5%)	44 (3%)	24 (4%)	34 (6%)
	SEVERE	3 (2%)	3 (1%)	9 (3%)	12 (1%)	6 (1%)	11 (2%)
Myalgia	N	151	357	359	1625	541	540
	ANY	30 (20%)	74 (21%)	117 (33%)	276 (17%)	95 (18%)	138 (26%)
	MILD	24 (16%)	48 (13%)	58 (16%)	201 (12%)	64 (12%)	94 (17%)
	MODERATE	5 (3%)	20 (6%)	45 (13%)	56 (3%)	25 (5%)	27 (5%)
	SEVERE	1 (1%)	6 (2%)	14 (4%)	19 (1%)	6 (1%)	17 (3%)
Arthralgia	N	151	357	359	1625	541	540
	ANY	7 (5%)	34 (10%)	55 (15%)	107 (7%)	51 (9%)	87 (16%)
	MILD	7 (5%)	20 (6%)	26 (7%)	82 (5%)	35 (6%)	56 (10%)
	MODERATE	0	7 (2%)	20 (6%)	19 (1%)	14 (3%)	20 (4%)
	SEVERE	0	7 (2%)	9 (3%)	6 (<1%)	2 (<1%)	11 (2%)
Headache	N	151	357	359	1625	541	540
	ANY	47 (31%)	106 (30%)	112 (31%)	372 (23%)	172 (32%)	194 (36%)
	MILD	35 (23%)	72 (20%)	64 (18%)	267 (16%)	99 (18%)	130 (24%)
	MODERATE	8 (5%)	21 (6%)	32 (9%)	87 (5%)	53 (10%)	37 (7%)
	SEVERE	4 (3%)	13 (4%)	16 (4%)	18 (1%)	20 (4%)	27 (5%)
Rash	N	0	0	0	1625	541	540
	ANY	0	0	0	28 (2%)	11 (2%)	14 (3%)
	OTHER	0	0	0	13 (1%)	1 (<1%)	0
	URTICARIAL	0	0	0	15 (1%)	10 (2%)	14 (3%)
Fever (>= 38C)	N	151	357	359	1616	541	540
	YES	0	8 (2%)	10 (3%)	18 (1%)	14 (3%)	21 (4%)
	NO	151 (100%)	349 (98%)	349 (97%)	1598 (99%)	527 (97%)	519 (96%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D13

Table 20

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
OTHER							
Stayed Home	N	150	357	358	1611	509	513
	YES	5 (3%)	8 (2%)	10 (3%)	38 (2%)	38 (7%)	51 (10%)
	NO	145 (97%)	349 (98%)	348 (97%)	1573 (98%)	471 (93%)	462 (90%)
Analgesic Antipyretics	N	151	357	359	1625	541	540
	YES	27 (18%)	19 (5%)	30 (8%)	221 (14%)	56 (10%)	86 (16%)
	NO	124 (82%)	338 (95%)	329 (92%)	1404 (86%)	485 (90%)	454 (84%)
Temperature (C)	N	151	357	359	1616	541	540
	<38 C	151 (100%)	349 (98%)	349 (97%)	1598 (99%)	527 (97%)	519 (96%)
	38 - 38.9 C	0	7 (2%)	9 (3%)	15 (1%)	13 (2%)	20 (4%)
	39.0 - 39.9 C	0	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)
	>= 40 C	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D13

Table 21

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
INJECTION SITE						
Pain	N	151	357	1623	541	503
	ANY	81 (54%)	114 (32%)	697 (43%)	234 (43%)	235 (47%)
	MILD	67 (44%)	72 (20%)	550 (34%)	158 (29%)	150 (30%)
	MODERATE	14 (9%)	32 (9%)	133 (8%)	69 (13%)	71 (14%)
	SEVERE	0	10 (3%)	14 (1%)	7 (1%)	14 (3%)
Erythema (mm)	N	151	357	1624	541	503
	ANY	57 (38%)	66 (18%)	235 (14%)	61 (11%)	63 (13%)
	>0 - 25 mm	48 (32%)	60 (17%)	173 (11%)	56 (10%)	55 (11%)
	>25 - 50 mm	4 (3%)	6 (2%)	30 (2%)	3 (1%)	2 (<1%)
	> 50 mm	5 (3%)	0	32 (2%)	2 (<1%)	6 (1%)
Induration (mm)	N	151	357	1624	541	503
	ANY	34 (23%)	58 (16%)	191 (12%)	64 (12%)	62 (12%)
	>0 - 25 mm	25 (17%)	46 (13%)	132 (8%)	52 (10%)	51 (10%)
	>25 - 50 mm	3 (2%)	9 (3%)	32 (2%)	6 (1%)	6 (1%)
	> 50 mm	6 (4%)	3 (1%)	27 (2%)	6 (1%)	5 (1%)
SYSTEMIC						
Chills	N	151	357	1625	541	503
	ANY	16 (11%)	34 (10%)	107 (7%)	52 (10%)	42 (8%)
	MILD	11 (7%)	22 (6%)	78 (5%)	35 (6%)	30 (6%)
	MODERATE	3 (2%)	8 (2%)	23 (1%)	13 (2%)	7 (1%)
	SEVERE	2 (1%)	4 (1%)	6 (<1%)	4 (1%)	5 (1%)
Nausea	N	151	357	1625	541	503
	ANY	16 (11%)	20 (6%)	143 (9%)	57 (11%)	50 (10%)
	MILD	12 (8%)	13 (4%)	99 (6%)	36 (7%)	39 (8%)
	MODERATE	3 (2%)	5 (1%)	37 (2%)	19 (4%)	7 (1%)
	SEVERE	1 (1%)	2 (1%)	7 (<1%)	2 (<1%)	4 (1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D13

Table 21

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Malaise	N	151	357	1625	541	503
	ANY	15 (10%)	37 (10%)	147 (9%)	99 (18%)	77 (15%)
	MILD	9 (6%)	21 (6%)	91 (6%)	69 (13%)	50 (10%)
	MODERATE	3 (2%)	13 (4%)	44 (3%)	24 (4%)	16 (3%)
	SEVERE	3 (2%)	3 (1%)	12 (1%)	6 (1%)	11 (2%)
Myalgia	N	151	357	1625	541	503
	ANY	30 (20%)	74 (21%)	276 (17%)	95 (18%)	78 (16%)
	MILD	24 (16%)	48 (13%)	201 (12%)	64 (12%)	49 (10%)
	MODERATE	5 (3%)	20 (6%)	56 (3%)	25 (5%)	24 (5%)
	SEVERE	1 (1%)	6 (2%)	19 (1%)	6 (1%)	5 (1%)
Arthralgia	N	151	357	1625	541	503
	ANY	7 (5%)	34 (10%)	107 (7%)	51 (9%)	44 (9%)
	MILD	7 (5%)	20 (6%)	82 (5%)	35 (6%)	31 (6%)
	MODERATE	0	7 (2%)	19 (1%)	14 (3%)	12 (2%)
	SEVERE	0	7 (2%)	6 (<1%)	2 (<1%)	1 (<1%)
Headache	N	151	357	1625	541	503
	ANY	47 (31%)	106 (30%)	372 (23%)	172 (32%)	119 (24%)
	MILD	35 (23%)	72 (20%)	267 (16%)	99 (18%)	65 (13%)
	MODERATE	8 (5%)	21 (6%)	87 (5%)	53 (10%)	39 (8%)
	SEVERE	4 (3%)	13 (4%)	18 (1%)	20 (4%)	15 (3%)
Rash	N	0	0	1625	541	503
	ANY	0	0	28 (2%)	11 (2%)	12 (2%)
	OTHER	0	0	13 (1%)	1 (<1%)	2 (<1%)
	URTICARIAL	0	0	15 (1%)	10 (2%)	10 (2%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D13

Table 21

Summary of Reactogenicity on Days 1 to 3, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Fever (>= 38C)	N	151	357	1616	541	503
	YES	0	8 (2%)	18 (1%)	14 (3%)	19 (4%)
	NO	151 (100%)	349 (98%)	1598 (99%)	527 (97%)	484 (96%)
OTHER						
Stayed Home	N	150	357	1611	509	486
	YES	5 (3%)	8 (2%)	38 (2%)	38 (7%)	24 (5%)
	NO	145 (97%)	349 (98%)	1573 (98%)	471 (93%)	462 (95%)
Analgesic Antipyretics	N	151	357	1625	541	503
	YES	27 (18%)	19 (5%)	221 (14%)	56 (10%)	42 (8%)
	NO	124 (82%)	338 (95%)	1404 (86%)	485 (90%)	461 (92%)
Temperature (C)	N	151	357	1616	541	503
	<38 C	151 (100%)	349 (98%)	1598 (99%)	527 (97%)	484 (96%)
	38 - 38.9 C	0	7 (2%)	15 (1%)	13 (2%)	17 (3%)
	39.0 - 39.9 C	0	1 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
	>= 40 C	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D13.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D13

Table 22

Summary of Reactogenicity on Days 4 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
INJECTION SITE						
Pain	N	3496	1133	1458	6087	1743
	ANY	377 (11%)	138 (12%)	170 (12%)	685 (11%)	191 (11%)
	MILD	305 (9%)	113 (10%)	118 (8%)	536 (9%)	156 (9%)
	MODERATE	63 (2%)	20 (2%)	40 (3%)	123 (2%)	28 (2%)
	SEVERE	9 (<1%)	5 (<1%)	12 (1%)	26 (<1%)	7 (<1%)
Erythema (mm)	N	3495	1133	1454	6082	1741
	ANY	165 (5%)	65 (6%)	77 (5%)	307 (5%)	72 (4%)
	>0 - 25 mm	111 (3%)	39 (3%)	43 (3%)	193 (3%)	50 (3%)
	>25 - 50 mm	32 (1%)	9 (1%)	13 (1%)	54 (1%)	12 (1%)
	> 50 mm	22 (1%)	17 (2%)	21 (1%)	60 (1%)	10 (1%)
Induration (mm)	N	3496	1132	1453	6081	1742
	ANY	196 (6%)	58 (5%)	63 (4%)	317 (5%)	68 (4%)
	>0 - 25 mm	123 (4%)	34 (3%)	41 (3%)	198 (3%)	49 (3%)
	>25 - 50 mm	50 (1%)	12 (1%)	13 (1%)	75 (1%)	12 (1%)
	> 50 mm	23 (1%)	12 (1%)	9 (1%)	44 (1%)	7 (<1%)
SYSTEMIC						
Chills	N	3498	1135	1458	6091	1743
	ANY	122 (3%)	31 (3%)	37 (3%)	190 (3%)	51 (3%)
	MILD	78 (2%)	21 (2%)	23 (2%)	122 (2%)	36 (2%)
	MODERATE	35 (1%)	7 (1%)	9 (1%)	51 (1%)	13 (1%)
	SEVERE	9 (<1%)	3 (<1%)	5 (<1%)	17 (<1%)	2 (<1%)
Nausea	N	3499	1135	1458	6092	1743
	ANY	173 (5%)	47 (4%)	35 (2%)	255 (4%)	60 (3%)
	MILD	115 (3%)	28 (2%)	23 (2%)	166 (3%)	38 (2%)
	MODERATE	45 (1%)	15 (1%)	7 (<1%)	67 (1%)	16 (1%)
	SEVERE	13 (<1%)	4 (<1%)	5 (<1%)	22 (<1%)	6 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D47.SAS(WARTERO) 10JUL08, 08:45 SAS.9.1 - PINJSUM_ACWY_D47

Table 22

Summary of Reactogenicity on Days 4 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Malaise	N	3498	1135	1458	6091	1743
	ANY	197 (6%)	86 (8%)	110 (8%)	393 (6%)	136 (8%)
	MILD	122 (3%)	51 (4%)	58 (4%)	231 (4%)	79 (5%)
	MODERATE	57 (2%)	21 (2%)	36 (2%)	114 (2%)	44 (3%)
	SEVERE	18 (1%)	14 (1%)	16 (1%)	48 (1%)	13 (1%)
Myalgia	N	3498	1135	1458	6091	1743
	ANY	262 (7%)	59 (5%)	95 (7%)	416 (7%)	127 (7%)
	MILD	191 (5%)	33 (3%)	53 (4%)	277 (5%)	74 (4%)
	MODERATE	52 (1%)	19 (2%)	33 (2%)	104 (2%)	45 (3%)
	SEVERE	19 (1%)	7 (1%)	9 (1%)	35 (1%)	8 (<1%)
Arthralgia	N	3498	1135	1458	6091	1743
	ANY	166 (5%)	25 (2%)	60 (4%)	251 (4%)	76 (4%)
	MILD	124 (4%)	16 (1%)	34 (2%)	174 (3%)	48 (3%)
	MODERATE	30 (1%)	7 (1%)	18 (1%)	55 (1%)	22 (1%)
	SEVERE	12 (<1%)	2 (<1%)	8 (1%)	22 (<1%)	6 (<1%)
Headache	N	3498	1135	1458	6091	1743
	ANY	577 (16%)	154 (14%)	183 (13%)	914 (15%)	249 (14%)
	MILD	377 (11%)	93 (8%)	110 (8%)	580 (10%)	163 (9%)
	MODERATE	146 (4%)	42 (4%)	48 (3%)	236 (4%)	69 (4%)
	SEVERE	54 (2%)	19 (2%)	25 (2%)	98 (2%)	17 (1%)
Rash	N	2633	1134	1458	5225	1743
	ANY	49 (2%)	22 (2%)	26 (2%)	97 (2%)	24 (1%)
	OTHER	15 (1%)	4 (<1%)	6 (<1%)	25 (<1%)	7 (<1%)
	URTICARIAL	34 (1%)	18 (2%)	20 (1%)	72 (1%)	17 (1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D47.SAS(WARTER0) 10JUL08, 08:45 SAS.9.1 - PINJSUM_ACWY_D47

Table 22

Summary of Reactogenicity on Days 4 to 7, Comparing Total MenACWY[1] across Age Groups

Reaction		Number (%) of Subjects				
		Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SYSTEMIC						
Fever (>= 38C)	N	3449	1058	1382	5889	1636
	YES	34 (1%)	11 (1%)	15 (1%)	60 (1%)	17 (1%)
	NO	3415 (99%)	1047 (99%)	1367 (99%)	5829 (99%)	1619 (99%)
OTHER						
Stayed Home	N	3496	1132	1454	6082	1745
	YES	51 (1%)	15 (1%)	21 (1%)	87 (1%)	31 (2%)
	NO	3445 (99%)	1117 (99%)	1433 (99%)	5995 (99%)	1714 (98%)
Analgesic Antipyretics	N	3497	1132	1454	6083	1743
	YES	253 (7%)	105 (9%)	170 (12%)	528 (9%)	168 (10%)
	NO	3244 (93%)	1027 (91%)	1284 (88%)	5555 (91%)	1575 (90%)
Temperature (C)	N	3449	1058	1382	5889	1636
	<38 C	3415 (99%)	1047 (99%)	1367 (99%)	5829 (99%)	1619 (99%)
	38 - 38.9 C	22 (1%)	9 (1%)	12 (1%)	43 (1%)	14 (1%)
	39.0 - 39.9 C	10 (<1%)	2 (<1%)	1 (<1%)	13 (<1%)	3 (<1%)
	>= 40 C	2 (<1%)	0	2 (<1%)	4 (<1%)	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_D47.SAS(WARTERO) 10JUL08, 08:45 SAS.9.1 - PINJSUM_ACWY_D47

Table 23.1

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
INJECTION SITE									
Pain	N	150	209	357	353	1609	531	509	502
	ANY	11 (7%)	12 (6%)	44 (12%)	86 (24%)	173 (11%)	38 (7%)	59 (12%)	116 (23%)
	MILD	9 (6%)	8 (4%)	37 (10%)	70 (20%)	146 (9%)	34 (6%)	45 (9%)	80 (16%)
	MODERATE	2 (1%)	4 (2%)	6 (2%)	16 (5%)	22 (1%)	3 (1%)	13 (3%)	27 (5%)
	SEVERE	0	0	1 (<1%)	0	5 (<1%)	1 (<1%)	1 (<1%)	9 (2%)
Erythema (mm)	N	148	209	357	353	1610	531	509	502
	ANY	6 (4%)	3 (1%)	20 (6%)	41 (12%)	82 (5%)	21 (4%)	20 (4%)	28 (6%)
	>0 - 25 mm	5 (3%)	3 (1%)	14 (4%)	36 (10%)	46 (3%)	15 (3%)	17 (3%)	28 (6%)
	>25 - 50 mm	0	0	5 (1%)	4 (1%)	21 (1%)	4 (1%)	1 (<1%)	0
	> 50 mm	1 (1%)	0	1 (<1%)	1 (<1%)	15 (1%)	2 (<1%)	2 (<1%)	0
Induration (mm)	N	149	209	357	353	1610	531	509	502
	ANY	7 (5%)	0	30 (8%)	59 (17%)	81 (5%)	19 (4%)	24 (5%)	46 (9%)
	>0 - 25 mm	4 (3%)	0	18 (5%)	45 (13%)	46 (3%)	13 (2%)	19 (4%)	39 (8%)
	>25 - 50 mm	2 (1%)	0	10 (3%)	13 (4%)	23 (1%)	6 (1%)	4 (1%)	4 (1%)
	> 50 mm	1 (1%)	0	2 (1%)	1 (<1%)	12 (1%)	0	1 (<1%)	3 (1%)
SYSTEMIC									
Chills	N	150	209	357	353	1611	531	509	502
	ANY	9 (6%)	5 (2%)	19 (5%)	9 (3%)	41 (3%)	15 (3%)	23 (5%)	30 (6%)
	MILD	7 (5%)	2 (1%)	10 (3%)	8 (2%)	28 (2%)	13 (2%)	12 (2%)	24 (5%)
	MODERATE	2 (1%)	2 (1%)	6 (2%)	1 (<1%)	10 (1%)	1 (<1%)	9 (2%)	6 (1%)
	SEVERE	0	1 (<1%)	3 (1%)	0	3 (<1%)	1 (<1%)	2 (<1%)	0
Nausea	N	150	209	357	353	1612	531	509	502
	ANY	8 (5%)	11 (5%)	16 (4%)	12 (3%)	80 (5%)	18 (3%)	25 (5%)	37 (7%)
	MILD	5 (3%)	8 (4%)	11 (3%)	9 (3%)	52 (3%)	11 (2%)	15 (3%)	25 (5%)
	MODERATE	2 (1%)	2 (1%)	3 (1%)	3 (1%)	24 (1%)	4 (1%)	8 (2%)	11 (2%)
	SEVERE	1 (1%)	1 (<1%)	2 (1%)	0	4 (<1%)	3 (1%)	2 (<1%)	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_11_18_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_11_18_D47

Table 23.1

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
SYSTEMIC									
Malaise	N	150	209	357	353	1611	531	509	502
	ANY	12 (8%)	11 (5%)	14 (4%)	23 (7%)	63 (4%)	28 (5%)	35 (7%)	61 (12%)
	MILD	8 (5%)	5 (2%)	6 (2%)	17 (5%)	41 (3%)	15 (3%)	21 (4%)	43 (9%)
	MODERATE	4 (3%)	5 (2%)	5 (1%)	6 (2%)	18 (1%)	9 (2%)	12 (2%)	16 (3%)
	SEVERE	0	1 (<1%)	3 (1%)	0	4 (<1%)	4 (1%)	2 (<1%)	2 (<1%)
Myalgia	N	150	209	357	353	1611	531	509	502
	ANY	11 (7%)	14 (7%)	39 (11%)	37 (10%)	111 (7%)	36 (7%)	27 (5%)	55 (11%)
	MILD	10 (7%)	7 (3%)	26 (7%)	28 (8%)	84 (5%)	25 (5%)	19 (4%)	39 (8%)
	MODERATE	1 (1%)	7 (3%)	9 (3%)	8 (2%)	18 (1%)	10 (2%)	7 (1%)	11 (2%)
	SEVERE	0	0	4 (1%)	1 (<1%)	9 (1%)	1 (<1%)	1 (<1%)	5 (1%)
Arthralgia	N	150	209	357	353	1611	531	509	502
	ANY	8 (5%)	4 (2%)	19 (5%)	21 (6%)	63 (4%)	15 (3%)	24 (5%)	31 (6%)
	MILD	8 (5%)	1 (<1%)	13 (4%)	16 (5%)	48 (3%)	11 (2%)	18 (4%)	22 (4%)
	MODERATE	0	3 (1%)	1 (<1%)	5 (1%)	13 (1%)	4 (1%)	5 (1%)	7 (1%)
	SEVERE	0	0	5 (1%)	0	2 (<1%)	0	1 (<1%)	2 (<1%)
Headache	N	150	209	357	353	1611	531	509	502
	ANY	33 (22%)	45 (22%)	57 (16%)	48 (14%)	242 (15%)	77 (15%)	85 (17%)	110 (22%)
	MILD	22 (15%)	31 (15%)	40 (11%)	35 (10%)	168 (10%)	56 (11%)	53 (10%)	71 (14%)
	MODERATE	7 (5%)	12 (6%)	10 (3%)	10 (3%)	59 (4%)	19 (4%)	26 (5%)	26 (5%)
	SEVERE	4 (3%)	2 (1%)	7 (2%)	3 (1%)	15 (1%)	2 (<1%)	6 (1%)	13 (3%)
Rash	N	0	0	0	0	1611	531	509	502
	ANY	0	0	0	0	27 (2%)	12 (2%)	11 (2%)	12 (2%)
	OTHER	0	0	0	0	14 (1%)	5 (1%)	1 (<1%)	3 (1%)
	URTICARIAL	0	0	0	0	13 (1%)	7 (1%)	10 (2%)	9 (2%)
Fever (>= 38C)	N	150	209	356	353	1587	524	505	498
	YES	1 (1%)	4 (2%)	6 (2%)	0	7 (<1%)	1 (<1%)	8 (2%)	6 (1%)
	NO	149 (99%)	205 (98%)	350 (98%)	353 (100%)	1580 (100%)	523 (100%)	497 (98%)	492 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_11_18_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_11_18_D47

Table 23.1

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 11-18

Reaction		Number (%) of Subjects							
		P6 ACWY (N=151)	P6 Menomune (N=209)	P11 ACWY (N=357)	P11 Tdap (N=353)	P13 ACWY (N=1631)	P13 Menactra (N=539)	P18 ACWY (N=541)	P18 Tdap (N=539)
OTHER									
Stayed Home	N	149	209	357	353	1610	532	509	502
	YES	1 (1%)	2 (1%)	6 (2%)	3 (1%)	16 (1%)	6 (1%)	11 (2%)	15 (3%)
	NO	148 (99%)	207 (99%)	351 (98%)	350 (99%)	1594 (99%)	526 (99%)	498 (98%)	487 (97%)
Analgesic Antipyretics	N	149	208	357	353	1612	532	508	503
	YES	20 (13%)	36 (17%)	20 (6%)	11 (3%)	132 (8%)	48 (9%)	31 (6%)	38 (8%)
	NO	129 (87%)	172 (83%)	337 (94%)	342 (97%)	1480 (92%)	484 (91%)	477 (94%)	465 (92%)
Temperature (C)	N	150	209	356	353	1587	524	505	498
	<38 C	149 (99%)	205 (98%)	350 (98%)	353 (100%)	1580 (100%)	523 (100%)	497 (98%)	492 (99%)
	38 - 38.9 C	1 (1%)	4 (2%)	4 (1%)	0	4 (<1%)	1 (<1%)	5 (1%)	5 (1%)
	39.0 - 39.9 C	0	0	2 (1%)	0	3 (<1%)	0	3 (1%)	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_11_18_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_11_18_D47

Table 23.2

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
INJECTION SITE					
Pain	N	297	103	836	463
	ANY	54 (18%)	7 (7%)	84 (10%)	57 (12%)
	MILD	48 (16%)	6 (6%)	65 (8%)	44 (10%)
	MODERATE	6 (2%)	1 (1%)	14 (2%)	13 (3%)
	SEVERE	0	0	5 (1%)	0
Erythema (mm)	N	297	103	836	461
	ANY	26 (9%)	3 (3%)	39 (5%)	23 (5%)
	>0 - 25 mm	13 (4%)	2 (2%)	26 (3%)	16 (3%)
	>25 - 50 mm	3 (1%)	1 (1%)	6 (1%)	2 (<1%)
	> 50 mm	10 (3%)	0	7 (1%)	5 (1%)
Induration (mm)	N	297	103	835	462
	ANY	21 (7%)	0	37 (4%)	21 (5%)
	>0 - 25 mm	8 (3%)	0	26 (3%)	14 (3%)
	>25 - 50 mm	7 (2%)	0	5 (1%)	2 (<1%)
	> 50 mm	6 (2%)	0	6 (1%)	5 (1%)
SYSTEMIC					
Chills	N	297	103	838	464
	ANY	5 (2%)	3 (3%)	26 (3%)	16 (3%)
	MILD	3 (1%)	2 (2%)	18 (2%)	11 (2%)
	MODERATE	2 (1%)	1 (1%)	5 (1%)	4 (1%)
	SEVERE	0	0	3 (<1%)	1 (<1%)
Nausea	N	297	103	838	464
	ANY	13 (4%)	6 (6%)	34 (4%)	19 (4%)
	MILD	7 (2%)	4 (4%)	21 (3%)	11 (2%)
	MODERATE	4 (1%)	2 (2%)	11 (1%)	6 (1%)
	SEVERE	2 (1%)	0	2 (<1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D47

Table 23.2

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
SYSTEMIC					
Malaise	N	297	103	838	464
	ANY	10 (3%)	8 (8%)	76 (9%)	48 (10%)
	MILD	5 (2%)	4 (4%)	46 (5%)	30 (6%)
	MODERATE	4 (1%)	2 (2%)	17 (2%)	15 (3%)
	SEVERE	1 (<1%)	2 (2%)	13 (2%)	3 (1%)
Myalgia	N	297	103	838	464
	ANY	20 (7%)	9 (9%)	39 (5%)	28 (6%)
	MILD	15 (5%)	4 (4%)	18 (2%)	15 (3%)
	MODERATE	5 (2%)	4 (4%)	14 (2%)	12 (3%)
	SEVERE	0	1 (1%)	7 (1%)	1 (<1%)
Arthralgia	N	297	103	838	464
	ANY	6 (2%)	4 (4%)	19 (2%)	21 (5%)
	MILD	4 (1%)	2 (2%)	12 (1%)	13 (3%)
	MODERATE	2 (1%)	1 (1%)	5 (1%)	8 (2%)
	SEVERE	0	1 (1%)	2 (<1%)	0
Headache	N	297	103	838	464
	ANY	43 (14%)	10 (10%)	111 (13%)	69 (15%)
	MILD	27 (9%)	7 (7%)	66 (8%)	46 (10%)
	MODERATE	13 (4%)	3 (3%)	29 (3%)	20 (4%)
	SEVERE	3 (1%)	0	16 (2%)	3 (1%)
Rash	N	297	103	837	464
	ANY	4 (1%)	0	18 (2%)	5 (1%)
	OTHER	2 (1%)	0	2 (<1%)	1 (<1%)
	URTICARIAL	2 (1%)	0	16 (2%)	4 (1%)
Fever (>= 38C)	N	294	101	764	410
	YES	2 (1%)	1 (1%)	9 (1%)	7 (2%)
	NO	292 (99%)	100 (99%)	755 (99%)	403 (98%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D47

Table 23.2

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 19-34

Reaction		Number (%) of Subjects P13 ACWY (N=307)	P13 Menactra (N=105)	P17 ACWY (N=838)	P17 Menactra (N=464)
OTHER					
Stayed Home	N	297	103	835	463
	YES	0	2 (2%)	15 (2%)	9 (2%)
	NO	297 (100%)	101 (98%)	820 (98%)	454 (98%)
Analgesic Antipyretics	N	297	103	835	463
	YES	35 (12%)	10 (10%)	70 (8%)	30 (6%)
	NO	262 (88%)	93 (90%)	765 (92%)	433 (94%)
Temperature (C)	N	294	101	764	410
	<38 C	292 (99%)	100 (99%)	755 (99%)	403 (98%)
	38 - 38.9 C	1 (<1%)	1 (1%)	8 (1%)	5 (1%)
	39.0 - 39.9 C	1 (<1%)	0	1 (<1%)	2 (<1%)
	>= 40 C	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_19_34_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_19_34_D47

Table 23.3

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
INJECTION SITE					
Pain	N	709	229	749	417
	ANY	84 (12%)	31 (14%)	86 (11%)	58 (14%)
	MILD	69 (10%)	30 (13%)	49 (7%)	42 (10%)
	MODERATE	13 (2%)	1 (<1%)	27 (4%)	10 (2%)
	SEVERE	2 (<1%)	0	10 (1%)	6 (1%)
Erythema (mm)	N	709	229	745	417
	ANY	43 (6%)	10 (4%)	34 (5%)	15 (4%)
	>0 - 25 mm	18 (3%)	7 (3%)	25 (3%)	10 (2%)
	>25 - 50 mm	9 (1%)	1 (<1%)	4 (1%)	4 (1%)
	> 50 mm	16 (2%)	2 (1%)	5 (1%)	1 (<1%)
Induration (mm)	N	709	229	744	417
	ANY	34 (5%)	12 (5%)	29 (4%)	16 (4%)
	>0 - 25 mm	18 (3%)	10 (4%)	23 (3%)	12 (3%)
	>25 - 50 mm	11 (2%)	2 (1%)	2 (<1%)	2 (<1%)
	> 50 mm	5 (1%)	0	4 (1%)	2 (<1%)
SYSTEMIC					
Chills	N	709	229	749	416
	ANY	8 (1%)	1 (<1%)	29 (4%)	16 (4%)
	MILD	6 (1%)	0	17 (2%)	10 (2%)
	MODERATE	2 (<1%)	1 (<1%)	7 (1%)	6 (1%)
	SEVERE	0	0	5 (1%)	0
Nausea	N	709	229	749	416
	ANY	14 (2%)	3 (1%)	21 (3%)	14 (3%)
	MILD	9 (1%)	2 (1%)	14 (2%)	10 (2%)
	MODERATE	4 (1%)	1 (<1%)	3 (<1%)	3 (1%)
	SEVERE	1 (<1%)	0	4 (1%)	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_35_55_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_35_55_D47

Table 23.3

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
SYSTEMIC					
Malaise	N	709	229	749	416
	ANY	26 (4%)	9 (4%)	84 (11%)	43 (10%)
	MILD	12 (2%)	5 (2%)	46 (6%)	25 (6%)
	MODERATE	10 (1%)	3 (1%)	26 (3%)	15 (4%)
	SEVERE	4 (1%)	1 (<1%)	12 (2%)	3 (1%)
Myalgia	N	709	229	749	416
	ANY	43 (6%)	12 (5%)	52 (7%)	42 (10%)
	MILD	29 (4%)	9 (4%)	24 (3%)	21 (5%)
	MODERATE	11 (2%)	2 (1%)	22 (3%)	17 (4%)
	SEVERE	3 (<1%)	1 (<1%)	6 (1%)	4 (1%)
Arthralgia	N	709	229	749	416
	ANY	23 (3%)	7 (3%)	37 (5%)	29 (7%)
	MILD	14 (2%)	5 (2%)	20 (3%)	17 (4%)
	MODERATE	6 (1%)	1 (<1%)	12 (2%)	8 (2%)
	SEVERE	3 (<1%)	1 (<1%)	5 (1%)	4 (1%)
Headache	N	709	229	749	416
	ANY	78 (11%)	31 (14%)	105 (14%)	62 (15%)
	MILD	50 (7%)	17 (7%)	60 (8%)	37 (9%)
	MODERATE	20 (3%)	12 (5%)	28 (4%)	15 (4%)
	SEVERE	8 (1%)	2 (1%)	17 (2%)	10 (2%)
Rash	N	709	229	749	416
	ANY	11 (2%)	1 (<1%)	15 (2%)	6 (1%)
	OTHER	3 (<1%)	1 (<1%)	3 (<1%)	0
	URTICARIAL	8 (1%)	0	12 (2%)	6 (1%)
Fever (>= 38C)	N	705	228	677	373
	YES	2 (<1%)	0	13 (2%)	8 (2%)
	NO	703 (100%)	228 (100%)	664 (98%)	365 (98%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONT_35_55_D47.SAS(WARTERO) 10JUL08, 08:49 SAS.9.1 - PINJSUM_MEN_CONT_35_55_D47

Table 23.3

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs. Controls by Study within Age Group
Ages 35-55

Reaction		Number (%) of Subjects P13 ACWY (N=711)	P13 Menactra (N=231)	P17 ACWY (N=750)	P17 Menactra (N=418)
OTHER					
Stayed Home	N	708	230	746	417
	YES	4 (1%)	0	17 (2%)	14 (3%)
	NO	704 (99%)	230 (100%)	729 (98%)	403 (97%)
Analgesic Antipyretics	N	709	229	745	416
	YES	104 (15%)	36 (16%)	66 (9%)	44 (11%)
	NO	605 (85%)	193 (84%)	679 (91%)	372 (89%)
Temperature (C)	N	705	228	677	373
	<38 C	703 (100%)	228 (100%)	664 (98%)	365 (98%)
	38 - 38.9 C	2 (<1%)	0	10 (1%)	7 (2%)
	39.0 - 39.9 C	0	0	1 (<1%)	1 (<1%)
	>= 40 C	0	0	2 (<1%)	0

Table 24

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
INJECTION SITE							
Pain	N	150	357	358	1609	509	513
	ANY	11 (7%)	44 (12%)	25 (7%)	173 (11%)	59 (12%)	65 (13%)
	MILD	9 (6%)	37 (10%)	20 (6%)	146 (9%)	45 (9%)	48 (9%)
	MODERATE	2 (1%)	6 (2%)	5 (1%)	22 (1%)	13 (3%)	15 (3%)
	SEVERE	0	1 (<1%)	0	5 (<1%)	1 (<1%)	2 (<1%)
Erythema (mm)	N	148	357	358	1610	509	513
	ANY	6 (4%)	20 (6%)	17 (5%)	82 (5%)	20 (4%)	20 (4%)
	>0 - 25 mm	5 (3%)	14 (4%)	14 (4%)	46 (3%)	17 (3%)	15 (3%)
	>25 - 50 mm	0	5 (1%)	2 (1%)	21 (1%)	1 (<1%)	3 (1%)
	> 50 mm	1 (1%)	1 (<1%)	1 (<1%)	15 (1%)	2 (<1%)	2 (<1%)
Induration (mm)	N	149	357	358	1610	509	513
	ANY	7 (5%)	30 (8%)	21 (6%)	81 (5%)	24 (5%)	33 (6%)
	>0 - 25 mm	4 (3%)	18 (5%)	13 (4%)	46 (3%)	19 (4%)	23 (4%)
	>25 - 50 mm	2 (1%)	10 (3%)	7 (2%)	23 (1%)	4 (1%)	4 (1%)
	> 50 mm	1 (1%)	2 (1%)	1 (<1%)	12 (1%)	1 (<1%)	6 (1%)
SYSTEMIC							
Chills	N	150	357	358	1611	509	513
	ANY	9 (6%)	19 (5%)	12 (3%)	41 (3%)	23 (5%)	18 (4%)
	MILD	7 (5%)	10 (3%)	9 (3%)	28 (2%)	12 (2%)	12 (2%)
	MODERATE	2 (1%)	6 (2%)	3 (1%)	10 (1%)	9 (2%)	5 (1%)
	SEVERE	0	3 (1%)	0	3 (<1%)	2 (<1%)	1 (<1%)
Nausea	N	150	357	358	1612	509	513
	ANY	8 (5%)	16 (4%)	13 (4%)	80 (5%)	25 (5%)	31 (6%)
	MILD	5 (3%)	11 (3%)	11 (3%)	52 (3%)	15 (3%)	21 (4%)
	MODERATE	2 (1%)	3 (1%)	1 (<1%)	24 (1%)	8 (2%)	7 (1%)
	SEVERE	1 (1%)	2 (1%)	1 (<1%)	4 (<1%)	2 (<1%)	3 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D47

Table 24

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
SYSTEMIC							
Malaise	N	150	357	358	1611	509	513
	ANY	12 (8%)	14 (4%)	24 (7%)	63 (4%)	35 (7%)	49 (10%)
	MILD	8 (5%)	6 (2%)	16 (4%)	41 (3%)	21 (4%)	30 (6%)
	MODERATE	4 (3%)	5 (1%)	6 (2%)	18 (1%)	12 (2%)	12 (2%)
	SEVERE	0	3 (1%)	2 (1%)	4 (<1%)	2 (<1%)	7 (1%)
Myalgia	N	150	357	358	1611	509	513
	ANY	11 (7%)	39 (11%)	36 (10%)	111 (7%)	27 (5%)	38 (7%)
	MILD	10 (7%)	26 (7%)	24 (7%)	84 (5%)	19 (4%)	28 (5%)
	MODERATE	1 (1%)	9 (3%)	8 (2%)	18 (1%)	7 (1%)	9 (2%)
	SEVERE	0	4 (1%)	4 (1%)	9 (1%)	1 (<1%)	1 (<1%)
Arthralgia	N	150	357	358	1611	509	513
	ANY	8 (5%)	19 (5%)	19 (5%)	63 (4%)	24 (5%)	33 (6%)
	MILD	8 (5%)	13 (4%)	13 (4%)	48 (3%)	18 (4%)	24 (5%)
	MODERATE	0	1 (<1%)	4 (1%)	13 (1%)	5 (1%)	7 (1%)
	SEVERE	0	5 (1%)	2 (1%)	2 (<1%)	1 (<1%)	2 (<1%)
Headache	N	150	357	358	1611	509	513
	ANY	33 (22%)	57 (16%)	57 (16%)	242 (15%)	85 (17%)	103 (20%)
	MILD	22 (15%)	40 (11%)	29 (8%)	168 (10%)	53 (10%)	65 (13%)
	MODERATE	7 (5%)	10 (3%)	15 (4%)	59 (4%)	26 (5%)	29 (6%)
	SEVERE	4 (3%)	7 (2%)	13 (4%)	15 (1%)	6 (1%)	9 (2%)
Rash	N	0	0	0	1611	509	513
	ANY	0	0	0	27 (2%)	11 (2%)	11 (2%)
	OTHER	0	0	0	14 (1%)	1 (<1%)	0
	URTICARIAL	0	0	0	13 (1%)	10 (2%)	11 (2%)
Fever (>= 38C)	N	150	356	357	1587	505	494
	YES	1 (1%)	6 (2%)	1 (<1%)	7 (<1%)	8 (2%)	11 (2%)
	NO	149 (99%)	350 (98%)	356 (100%)	1580 (100%)	497 (98%)	483 (98%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D47

Table 24

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects					
		P6 ACWY (N=151)	P11 ACWY (N=357)	P11 ACWY+Tdap (N=359)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 ACWY+HPV+Tdap (N=540)
OTHER							
Stayed Home	N	149	357	358	1610	509	513
	YES	1 (1%)	6 (2%)	3 (1%)	16 (1%)	11 (2%)	14 (3%)
	NO	148 (99%)	351 (98%)	355 (99%)	1594 (99%)	498 (98%)	499 (97%)
Analgesic Antipyretics	N	149	357	358	1612	508	513
	YES	20 (13%)	20 (6%)	18 (5%)	132 (8%)	31 (6%)	32 (6%)
	NO	129 (87%)	337 (94%)	340 (95%)	1480 (92%)	477 (94%)	481 (94%)
Temperature (C)	N	150	356	357	1587	505	494
	<38 C	149 (99%)	350 (98%)	356 (100%)	1580 (100%)	497 (98%)	483 (98%)
	38 - 38.9 C	1 (1%)	4 (1%)	0	4 (<1%)	5 (1%)	8 (2%)
	39.0 - 39.9 C	0	2 (1%)	1 (<1%)	3 (<1%)	3 (1%)	1 (<1%)
	>= 40 C	0	0	0	0	0	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_CONVAC_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_CONVAC_11_18_D47

Table 25

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
INJECTION SITE						
Pain	N	150	357	1609	509	485
	ANY	11 (7%)	44 (12%)	173 (11%)	59 (12%)	50 (10%)
	MILD	9 (6%)	37 (10%)	146 (9%)	45 (9%)	35 (7%)
	MODERATE	2 (1%)	6 (2%)	22 (1%)	13 (3%)	11 (2%)
	SEVERE	0	1 (<1%)	5 (<1%)	1 (<1%)	4 (1%)
Erythema (mm)	N	148	357	1610	509	484
	ANY	6 (4%)	20 (6%)	82 (5%)	20 (4%)	18 (4%)
	>0 - 25 mm	5 (3%)	14 (4%)	46 (3%)	17 (3%)	16 (3%)
	>25 - 50 mm	0	5 (1%)	21 (1%)	1 (<1%)	0
	> 50 mm	1 (1%)	1 (<1%)	15 (1%)	2 (<1%)	2 (<1%)
Induration (mm)	N	149	357	1610	509	485
	ANY	7 (5%)	30 (8%)	81 (5%)	24 (5%)	23 (5%)
	>0 - 25 mm	4 (3%)	18 (5%)	46 (3%)	19 (4%)	19 (4%)
	>25 - 50 mm	2 (1%)	10 (3%)	23 (1%)	4 (1%)	1 (<1%)
	> 50 mm	1 (1%)	2 (1%)	12 (1%)	1 (<1%)	3 (1%)
SYSTEMIC						
Chills	N	150	357	1611	509	485
	ANY	9 (6%)	19 (5%)	41 (3%)	23 (5%)	11 (2%)
	MILD	7 (5%)	10 (3%)	28 (2%)	12 (2%)	9 (2%)
	MODERATE	2 (1%)	6 (2%)	10 (1%)	9 (2%)	1 (<1%)
	SEVERE	0	3 (1%)	3 (<1%)	2 (<1%)	1 (<1%)
Nausea	N	150	357	1612	509	485
	ANY	8 (5%)	16 (4%)	80 (5%)	25 (5%)	29 (6%)
	MILD	5 (3%)	11 (3%)	52 (3%)	15 (3%)	22 (5%)
	MODERATE	2 (1%)	3 (1%)	24 (1%)	8 (2%)	5 (1%)
	SEVERE	1 (1%)	2 (1%)	4 (<1%)	2 (<1%)	2 (<1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D47

Table 25

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Malaise	N	150	357	1611	509	485
	ANY	12 (8%)	14 (4%)	63 (4%)	35 (7%)	39 (8%)
	MILD	8 (5%)	6 (2%)	41 (3%)	21 (4%)	27 (6%)
	MODERATE	4 (3%)	5 (1%)	18 (1%)	12 (2%)	8 (2%)
	SEVERE	0	3 (1%)	4 (<1%)	2 (<1%)	4 (1%)
Myalgia	N	150	357	1611	509	485
	ANY	11 (7%)	39 (11%)	111 (7%)	27 (5%)	23 (5%)
	MILD	10 (7%)	26 (7%)	84 (5%)	19 (4%)	14 (3%)
	MODERATE	1 (1%)	9 (3%)	18 (1%)	7 (1%)	6 (1%)
	SEVERE	0	4 (1%)	9 (1%)	1 (<1%)	3 (1%)
Arthralgia	N	150	357	1611	509	484
	ANY	8 (5%)	19 (5%)	63 (4%)	24 (5%)	18 (4%)
	MILD	8 (5%)	13 (4%)	48 (3%)	18 (4%)	13 (3%)
	MODERATE	0	1 (<1%)	13 (1%)	5 (1%)	5 (1%)
	SEVERE	0	5 (1%)	2 (<1%)	1 (<1%)	0
Headache	N	150	357	1611	509	485
	ANY	33 (22%)	57 (16%)	242 (15%)	85 (17%)	67 (14%)
	MILD	22 (15%)	40 (11%)	168 (10%)	53 (10%)	44 (9%)
	MODERATE	7 (5%)	10 (3%)	59 (4%)	26 (5%)	16 (3%)
	SEVERE	4 (3%)	7 (2%)	15 (1%)	6 (1%)	7 (1%)
Rash	N	0	0	1611	509	485
	ANY	0	0	27 (2%)	11 (2%)	8 (2%)
	OTHER	0	0	14 (1%)	1 (<1%)	1 (<1%)
	URTICARIAL	0	0	13 (1%)	10 (2%)	7 (1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D47

Table 25

Summary of Reactogenicity on Days 4 to 7, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects P6 ACWY (N=151)	P11 ACWY (N=357)	P13 ACWY (N=1631)	P18 ACWY (N=541)	P18 Tdap, ACWY (N=503)
SYSTEMIC						
Fever (>= 38C)	N	150	356	1587	505	483
	YES	1 (1%)	6 (2%)	7 (<1%)	8 (2%)	14 (3%)
	NO	149 (99%)	350 (98%)	1580 (100%)	497 (98%)	469 (97%)
OTHER						
Stayed Home	N	149	357	1610	509	485
	YES	1 (1%)	6 (2%)	16 (1%)	11 (2%)	6 (1%)
	NO	148 (99%)	351 (98%)	1594 (99%)	498 (98%)	479 (99%)
Analgesic Antipyretics	N	149	357	1612	508	485
	YES	20 (13%)	20 (6%)	132 (8%)	31 (6%)	20 (4%)
	NO	129 (87%)	337 (94%)	1480 (92%)	477 (94%)	465 (96%)
Temperature (C)	N	150	356	1587	505	483
	<38 C	149 (99%)	350 (98%)	1580 (100%)	497 (98%)	469 (97%)
	38 - 38.9 C	1 (1%)	4 (1%)	4 (<1%)	5 (1%)	10 (2%)
	39.0 - 39.9 C	0	2 (1%)	3 (<1%)	3 (1%)	4 (1%)
	>= 40 C	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MEN_TDAP_11_18_D47.SAS(WARTERO) 10JUL08, 08:50 SAS.9.1 - PINJSUM_MEN_TDAP_11_18_D47

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=3579)	6HR (N=3579)	DAY 2 (N=3579)	DAY 3 (N=3579)	DAY 4 (N=3579)	DAY 5 (N=3579)	DAY 6 (N=3579)	DAY 7 (N=3579)
INJECTION SITE									
Pain	N	3570	3493	3496	3497	3494	3494	3495	3493
	ANY	474 (13%)	592 (17%)	302 (9%)	95 (3%)	23 (1%)	11 (<1%)	3 (<1%)	1 (<1%)
	MILD	408 (11%)	476 (14%)	249 (7%)	87 (2%)	18 (1%)	11 (<1%)	2 (<1%)	1 (<1%)
	MODERATE	58 (2%)	110 (3%)	46 (1%)	6 (<1%)	4 (<1%)	0	1 (<1%)	0
	SEVERE	8 (<1%)	6 (<1%)	7 (<1%)	2 (<1%)	1 (<1%)	0	0	0
Erythema (mm)	N	3571	3491	3496	3496	3494	3495	3494	3491
	ANY	209 (6%)	141 (4%)	114 (3%)	66 (2%)	13 (<1%)	5 (<1%)	4 (<1%)	0
	>0 - 25 mm	203 (6%)	135 (4%)	82 (2%)	38 (1%)	9 (<1%)	4 (<1%)	4 (<1%)	0
	>25 - 50 mm	6 (<1%)	2 (<1%)	18 (1%)	20 (1%)	3 (<1%)	1 (<1%)	0	0
	> 50 mm	0	4 (<1%)	14 (<1%)	8 (<1%)	1 (<1%)	0	0	0
Induration (mm)	N	3571	3491	3496	3496	3495	3496	3495	3491
	ANY	98 (3%)	135 (4%)	150 (4%)	64 (2%)	13 (<1%)	5 (<1%)	2 (<1%)	1 (<1%)
	>0 - 25 mm	95 (3%)	117 (3%)	108 (3%)	34 (1%)	10 (<1%)	4 (<1%)	2 (<1%)	0
	>25 - 50 mm	2 (<1%)	12 (<1%)	25 (1%)	19 (1%)	2 (<1%)	0	0	1 (<1%)
	> 50 mm	1 (<1%)	6 (<1%)	17 (<1%)	11 (<1%)	1 (<1%)	1 (<1%)	0	0
SYSTEMIC									
Chills	N	3573	3496	3499	3499	3497	3498	3498	3495
	ANY	35 (1%)	99 (3%)	128 (4%)	44 (1%)	26 (1%)	21 (1%)	12 (<1%)	15 (<1%)
	MILD	29 (1%)	74 (2%)	81 (2%)	33 (1%)	18 (1%)	12 (<1%)	9 (<1%)	8 (<1%)
	MODERATE	5 (<1%)	20 (1%)	34 (1%)	9 (<1%)	6 (<1%)	9 (<1%)	3 (<1%)	6 (<1%)
	SEVERE	1 (<1%)	5 (<1%)	13 (<1%)	2 (<1%)	2 (<1%)	0	0	1 (<1%)
Nausea	N	3573	3497	3500	3500	3498	3499	3499	3496
	ANY	37 (1%)	115 (3%)	143 (4%)	49 (1%)	34 (1%)	22 (1%)	20 (1%)	20 (1%)
	MILD	32 (1%)	95 (3%)	101 (3%)	31 (1%)	24 (1%)	14 (<1%)	16 (<1%)	13 (<1%)
	MODERATE	4 (<1%)	18 (1%)	33 (1%)	12 (<1%)	9 (<1%)	6 (<1%)	2 (<1%)	6 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	9 (<1%)	6 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 11-18

Reaction		30M (N=3579)	6HR (N=3579)	DAY 2 (N=3579)	DAY 3 (N=3579)	DAY 4 (N=3579)	DAY 5 (N=3579)	DAY 6 (N=3579)	DAY 7 (N=3579)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	3573	3496	3499	3499	3497	3498	3498	3495
	ANY	50 (1%)	160 (5%)	196 (6%)	74 (2%)	20 (1%)	17 (<1%)	17 (<1%)	16 (<1%)
	MILD	43 (1%)	120 (3%)	123 (4%)	48 (1%)	15 (<1%)	11 (<1%)	11 (<1%)	9 (<1%)
	MODERATE	7 (<1%)	32 (1%)	56 (2%)	19 (1%)	5 (<1%)	4 (<1%)	6 (<1%)	7 (<1%)
	SEVERE	0	8 (<1%)	17 (<1%)	7 (<1%)	0	2 (<1%)	0	0
Myalgia	N	3573	3496	3499	3499	3497	3498	3498	3495
	ANY	100 (3%)	321 (9%)	228 (7%)	81 (2%)	18 (1%)	21 (1%)	13 (<1%)	9 (<1%)
	MILD	79 (2%)	236 (7%)	161 (5%)	64 (2%)	15 (<1%)	20 (1%)	8 (<1%)	5 (<1%)
	MODERATE	16 (<1%)	68 (2%)	48 (1%)	13 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)	4 (<1%)
	SEVERE	5 (<1%)	17 (<1%)	19 (1%)	4 (<1%)	0	0	1 (<1%)	0
Arthralgia	N	3573	3496	3499	3499	3497	3498	3498	3495
	ANY	36 (1%)	128 (4%)	129 (4%)	48 (1%)	13 (<1%)	20 (1%)	16 (<1%)	12 (<1%)
	MILD	30 (1%)	89 (3%)	94 (3%)	40 (1%)	11 (<1%)	15 (<1%)	11 (<1%)	9 (<1%)
	MODERATE	5 (<1%)	32 (1%)	24 (1%)	4 (<1%)	2 (<1%)	4 (<1%)	5 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	7 (<1%)	11 (<1%)	4 (<1%)	0	1 (<1%)	0	1 (<1%)
Headache	N	3573	3495	3499	3499	3497	3498	3497	3495
	ANY	176 (5%)	386 (11%)	331 (9%)	110 (3%)	80 (2%)	55 (2%)	45 (1%)	24 (1%)
	MILD	142 (4%)	297 (8%)	228 (7%)	76 (2%)	61 (2%)	43 (1%)	33 (1%)	16 (<1%)
	MODERATE	25 (1%)	71 (2%)	74 (2%)	25 (1%)	14 (<1%)	11 (<1%)	6 (<1%)	7 (<1%)
	SEVERE	9 (<1%)	18 (1%)	29 (1%)	9 (<1%)	5 (<1%)	1 (<1%)	6 (<1%)	1 (<1%)
Rash	N	2705	2631	2634	2634	2631	2632	2632	2630
	ANY	1 (<1%)	12 (<1%)	21 (1%)	19 (1%)	11 (<1%)	8 (<1%)	7 (<1%)	3 (<1%)
	OTHER	0	3 (<1%)	5 (<1%)	7 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	URTICARIAL	1 (<1%)	9 (<1%)	16 (1%)	12 (<1%)	8 (<1%)	6 (<1%)	5 (<1%)	1 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=3579)	6HR (N=3579)	DAY 2 (N=3579)	DAY 3 (N=3579)	DAY 4 (N=3579)	DAY 5 (N=3579)	DAY 6 (N=3579)	DAY 7 (N=3579)
SYSTEMIC									
Fever (>= 38C)	N	3563	3441	3452	3451	3431	3433	3428	3394
	YES	6 (<1%)	12 (<1%)	38 (1%)	15 (<1%)	7 (<1%)	9 (<1%)	4 (<1%)	5 (<1%)
	NO	3557 (100%)	3429 (100%)	3414 (99%)	3436 (100%)	3424 (100%)	3424 (100%)	3424 (100%)	3389 (100%)
OTHER									
Stayed Home	N	0	3496	3496	3496	3495	3493	3495	3492
	YES	0	61 (2%)	69 (2%)	20 (1%)	11 (<1%)	5 (<1%)	7 (<1%)	3 (<1%)
	NO	0	3435 (98%)	3427 (98%)	3476 (99%)	3484 (100%)	3488 (100%)	3488 (100%)	3489 (100%)
Analgesic Antipyretics	N	3573	3496	3497	3496	3496	3495	3495	3493
	YES	12 (<1%)	132 (4%)	229 (7%)	66 (2%)	48 (1%)	31 (1%)	31 (1%)	27 (1%)
	NO	3561 (100%)	3364 (96%)	3268 (93%)	3430 (98%)	3448 (99%)	3464 (99%)	3464 (99%)	3466 (99%)
Temperature (C)	N	3563	3441	3452	3451	3431	3433	3428	3394
	<38 C	3557 (100%)	3429 (100%)	3414 (99%)	3436 (100%)	3424 (100%)	3424 (100%)	3424 (100%)	3389 (100%)
	38 - 38.9 C	6 (<1%)	11 (<1%)	34 (1%)	14 (<1%)	6 (<1%)	7 (<1%)	4 (<1%)	2 (<1%)
	39.0 - 39.9 C	0	1 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	0	3 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 19-34

Reaction		Number (%) of Subjects							
		30M (N=1145)	6HR (N=1145)	DAY 2 (N=1145)	DAY 3 (N=1145)	DAY 4 (N=1145)	DAY 5 (N=1145)	DAY 6 (N=1145)	DAY 7 (N=1145)
INJECTION SITE									
Pain	N	1144	1132	1134	1134	1133	1132	1132	1130
	ANY	204 (18%)	167 (15%)	103 (9%)	23 (2%)	7 (1%)	4 (<1%)	0	2 (<1%)
	MILD	177 (15%)	140 (12%)	86 (8%)	20 (2%)	7 (1%)	3 (<1%)	0	2 (<1%)
	MODERATE	26 (2%)	24 (2%)	16 (1%)	3 (<1%)	0	1 (<1%)	0	0
	SEVERE	1 (<1%)	3 (<1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	1144	1132	1133	1132	1133	1132	1132	1130
	ANY	97 (8%)	22 (2%)	47 (4%)	11 (1%)	2 (<1%)	5 (<1%)	3 (<1%)	5 (<1%)
	>0 - 25 mm	94 (8%)	20 (2%)	37 (3%)	9 (1%)	1 (<1%)	2 (<1%)	2 (<1%)	4 (<1%)
	>25 - 50 mm	3 (<1%)	0	8 (1%)	1 (<1%)	0	3 (<1%)	1 (<1%)	0
	> 50 mm	0	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)
Induration (mm)	N	1144	1131	1132	1132	1132	1131	1131	1129
	ANY	50 (4%)	27 (2%)	48 (4%)	15 (1%)	2 (<1%)	4 (<1%)	3 (<1%)	1 (<1%)
	>0 - 25 mm	49 (4%)	25 (2%)	39 (3%)	10 (1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
	>25 - 50 mm	1 (<1%)	1 (<1%)	7 (1%)	4 (<1%)	0	2 (<1%)	1 (<1%)	0
	> 50 mm	0	1 (<1%)	2 (<1%)	1 (<1%)	0	0	0	0
SYSTEMIC									
Chills	N	1144	1133	1135	1135	1135	1135	1135	1133
	ANY	9 (1%)	17 (2%)	30 (3%)	8 (1%)	7 (1%)	3 (<1%)	4 (<1%)	1 (<1%)
	MILD	7 (1%)	15 (1%)	16 (1%)	6 (1%)	7 (1%)	1 (<1%)	3 (<1%)	1 (<1%)
	MODERATE	1 (<1%)	2 (<1%)	10 (1%)	0	0	1 (<1%)	1 (<1%)	0
	SEVERE	1 (<1%)	0	4 (<1%)	2 (<1%)	0	1 (<1%)	0	0
Nausea	N	1144	1133	1135	1135	1135	1135	1135	1133
	ANY	8 (1%)	33 (3%)	23 (2%)	8 (1%)	10 (1%)	11 (1%)	4 (<1%)	0
	MILD	6 (1%)	29 (3%)	16 (1%)	8 (1%)	7 (1%)	7 (1%)	4 (<1%)	0
	MODERATE	1 (<1%)	4 (<1%)	6 (1%)	0	3 (<1%)	2 (<1%)	0	0
	SEVERE	1 (<1%)	0	1 (<1%)	0	0	2 (<1%)	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 19-34

Reaction		30M (N=1145)	6HR (N=1145)	DAY 2 (N=1145)	DAY 3 (N=1145)	DAY 4 (N=1145)	DAY 5 (N=1145)	DAY 6 (N=1145)	DAY 7 (N=1145)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	1144	1133	1135	1135	1135	1135	1135	1133
	ANY	16 (1%)	56 (5%)	84 (7%)	19 (2%)	10 (1%)	8 (1%)	9 (1%)	3 (<1%)
	MILD	13 (1%)	51 (5%)	52 (5%)	13 (1%)	7 (1%)	5 (<1%)	7 (1%)	2 (<1%)
	MODERATE	2 (<1%)	2 (<1%)	26 (2%)	3 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	SEVERE	1 (<1%)	3 (<1%)	6 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0
Myalgia	N	1144	1133	1135	1135	1135	1135	1135	1133
	ANY	10 (1%)	45 (4%)	69 (6%)	22 (2%)	4 (<1%)	5 (<1%)	3 (<1%)	2 (<1%)
	MILD	8 (1%)	38 (3%)	45 (4%)	18 (2%)	4 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
	MODERATE	2 (<1%)	5 (<1%)	20 (2%)	1 (<1%)	0	3 (<1%)	1 (<1%)	0
	SEVERE	0	2 (<1%)	4 (<1%)	3 (<1%)	0	0	1 (<1%)	0
Arthralgia	N	1144	1132	1134	1135	1135	1135	1135	1133
	ANY	2 (<1%)	19 (2%)	28 (2%)	15 (1%)	2 (<1%)	3 (<1%)	4 (<1%)	1 (<1%)
	MILD	2 (<1%)	14 (1%)	20 (2%)	11 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)
	MODERATE	0	4 (<1%)	5 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	1 (<1%)	3 (<1%)	1 (<1%)	0	0	0	0
Headache	N	1144	1133	1135	1135	1135	1135	1135	1133
	ANY	30 (3%)	104 (9%)	91 (8%)	37 (3%)	30 (3%)	9 (1%)	10 (1%)	5 (<1%)
	MILD	24 (2%)	82 (7%)	64 (6%)	25 (2%)	19 (2%)	6 (1%)	8 (1%)	5 (<1%)
	MODERATE	6 (1%)	18 (2%)	23 (2%)	10 (1%)	9 (1%)	3 (<1%)	1 (<1%)	0
	SEVERE	0	4 (<1%)	4 (<1%)	2 (<1%)	2 (<1%)	0	1 (<1%)	0
Rash	N	1144	1133	1135	1135	1134	1134	1134	1132
	ANY	4 (<1%)	9 (1%)	9 (1%)	5 (<1%)	6 (1%)	3 (<1%)	1 (<1%)	2 (<1%)
	OTHER	2 (<1%)	3 (<1%)	5 (<1%)	2 (<1%)	1 (<1%)	0	0	0
	URTICARIAL	2 (<1%)	6 (1%)	4 (<1%)	3 (<1%)	5 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 19-34

Reaction		Number (%) of Subjects							
		30M (N=1145)	6HR (N=1145)	DAY 2 (N=1145)	DAY 3 (N=1145)	DAY 4 (N=1145)	DAY 5 (N=1145)	DAY 6 (N=1145)	DAY 7 (N=1145)
SYSTEMIC									
Fever (>= 38C)	N	1143	1061	1064	1060	1057	1054	1055	1044
	YES	1 (<1%)	6 (1%)	9 (1%)	7 (1%)	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
	NO	1142 (100%)	1055 (99%)	1055 (99%)	1053 (99%)	1055 (100%)	1053 (100%)	1052 (100%)	1042 (100%)
OTHER									
Stayed Home	N	0	1131	1132	1133	1132	1132	1132	1129
	YES	0	14 (1%)	20 (2%)	7 (1%)	4 (<1%)	0	1 (<1%)	1 (<1%)
	NO	0	1117 (99%)	1112 (98%)	1126 (99%)	1128 (100%)	1132 (100%)	1131 (100%)	1128 (100%)
Analgesic Antipyretics	N	1143	1131	1132	1132	1132	1130	1130	1127
	YES	8 (1%)	51 (5%)	72 (6%)	29 (3%)	20 (2%)	13 (1%)	9 (1%)	6 (1%)
	NO	1135 (99%)	1080 (95%)	1060 (94%)	1103 (97%)	1112 (98%)	1117 (99%)	1121 (99%)	1121 (99%)
Temperature (C)	N	1143	1061	1064	1060	1057	1054	1055	1044
	<38 C	1142 (100%)	1055 (99%)	1055 (99%)	1053 (99%)	1055 (100%)	1053 (100%)	1052 (100%)	1042 (100%)
	38 - 38.9 C	1 (<1%)	4 (<1%)	6 (1%)	4 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	39.0 - 39.9 C	0	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)	0
	>= 40 C	0	0	1 (<1%)	1 (<1%)	0	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 35-55

Reaction		Number (%) of Subjects							
		30M (N=1461)	6HR (N=1461)	DAY 2 (N=1461)	DAY 3 (N=1461)	DAY 4 (N=1461)	DAY 5 (N=1461)	DAY 6 (N=1461)	DAY 7 (N=1461)
INJECTION SITE									
Pain	N	1461	1432	1456	1459	1457	1456	1455	1453
	ANY	195 (13%)	143 (10%)	113 (8%)	38 (3%)	8 (1%)	5 (<1%)	6 (<1%)	5 (<1%)
	MILD	164 (11%)	119 (8%)	95 (7%)	27 (2%)	6 (<1%)	4 (<1%)	5 (<1%)	2 (<1%)
	MODERATE	30 (2%)	22 (2%)	14 (1%)	10 (1%)	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Erythema (mm)	N	1461	1429	1451	1454	1453	1452	1452	1450
	ANY	71 (5%)	42 (3%)	42 (3%)	13 (1%)	6 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)
	>0 - 25 mm	69 (5%)	36 (3%)	33 (2%)	9 (1%)	3 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
	>25 - 50 mm	2 (<1%)	5 (<1%)	8 (1%)	2 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	0
	> 50 mm	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0	2 (<1%)	0
Induration (mm)	N	1461	1430	1452	1454	1452	1452	1451	1449
	ANY	55 (4%)	35 (2%)	45 (3%)	9 (1%)	5 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)
	>0 - 25 mm	55 (4%)	28 (2%)	35 (2%)	7 (<1%)	4 (<1%)	2 (<1%)	5 (<1%)	0
	>25 - 50 mm	0	5 (<1%)	8 (1%)	2 (<1%)	1 (<1%)	0	0	0
	> 50 mm	0	2 (<1%)	2 (<1%)	0	0	0	0	1 (<1%)
SYSTEMIC									
Chills	N	1461	1433	1457	1458	1457	1457	1457	1455
	ANY	1 (<1%)	23 (2%)	25 (2%)	12 (1%)	8 (1%)	6 (<1%)	6 (<1%)	5 (<1%)
	MILD	1 (<1%)	17 (1%)	13 (1%)	11 (1%)	5 (<1%)	6 (<1%)	2 (<1%)	3 (<1%)
	MODERATE	0	4 (<1%)	11 (1%)	1 (<1%)	2 (<1%)	0	3 (<1%)	2 (<1%)
	SEVERE	0	2 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Nausea	N	1461	1433	1457	1458	1457	1457	1457	1455
	ANY	5 (<1%)	21 (1%)	26 (2%)	16 (1%)	8 (1%)	7 (<1%)	4 (<1%)	1 (<1%)
	MILD	4 (<1%)	19 (1%)	20 (1%)	10 (1%)	6 (<1%)	6 (<1%)	2 (<1%)	0
	MODERATE	1 (<1%)	2 (<1%)	5 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	0	0
	SEVERE	0	0	1 (<1%)	0	1 (<1%)	0	2 (<1%)	1 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 35-55

Reaction		30M (N=1461)	6HR (N=1461)	DAY 2 (N=1461)	DAY 3 (N=1461)	DAY 4 (N=1461)	DAY 5 (N=1461)	DAY 6 (N=1461)	DAY 7 (N=1461)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	1461	1433	1457	1458	1457	1457	1457	1455
	ANY	11 (1%)	45 (3%)	69 (5%)	35 (2%)	18 (1%)	10 (1%)	10 (1%)	8 (1%)
	MILD	9 (1%)	33 (2%)	45 (3%)	22 (2%)	9 (1%)	6 (<1%)	5 (<1%)	5 (<1%)
	MODERATE	1 (<1%)	9 (1%)	21 (1%)	12 (1%)	7 (<1%)	4 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)	0	3 (<1%)	1 (<1%)
Myalgia	N	1461	1434	1457	1458	1457	1457	1457	1455
	ANY	9 (1%)	41 (3%)	64 (4%)	24 (2%)	12 (1%)	12 (1%)	9 (1%)	8 (1%)
	MILD	8 (1%)	32 (2%)	42 (3%)	11 (1%)	9 (1%)	9 (1%)	6 (<1%)	6 (<1%)
	MODERATE	0	7 (<1%)	18 (1%)	13 (1%)	2 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	4 (<1%)	0	1 (<1%)	0	2 (<1%)	0
Arthralgia	N	1461	1433	1457	1458	1457	1457	1457	1455
	ANY	7 (<1%)	18 (1%)	39 (3%)	16 (1%)	11 (1%)	7 (<1%)	3 (<1%)	3 (<1%)
	MILD	6 (<1%)	13 (1%)	26 (2%)	12 (1%)	5 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
	MODERATE	0	2 (<1%)	10 (1%)	4 (<1%)	5 (<1%)	4 (<1%)	0	1 (<1%)
	SEVERE	1 (<1%)	3 (<1%)	3 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Headache	N	1461	1434	1457	1458	1457	1457	1457	1456
	ANY	41 (3%)	93 (6%)	93 (6%)	58 (4%)	26 (2%)	18 (1%)	20 (1%)	9 (1%)
	MILD	37 (3%)	68 (5%)	61 (4%)	41 (3%)	18 (1%)	8 (1%)	13 (1%)	6 (<1%)
	MODERATE	2 (<1%)	19 (1%)	23 (2%)	16 (1%)	3 (<1%)	7 (<1%)	7 (<1%)	3 (<1%)
	SEVERE	2 (<1%)	6 (<1%)	9 (1%)	1 (<1%)	5 (<1%)	3 (<1%)	0	0
Rash	N	1461	1433	1457	1458	1457	1457	1457	1455
	ANY	2 (<1%)	7 (<1%)	7 (<1%)	10 (1%)	6 (<1%)	3 (<1%)	2 (<1%)	2 (<1%)
	OTHER	0	3 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)	0	1 (<1%)	0
	URTICARIAL	2 (<1%)	4 (<1%)	6 (<1%)	5 (<1%)	5 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Ages 35-55

Reaction		Number (%) of Subjects							
		30M (N=1461)	6HR (N=1461)	DAY 2 (N=1461)	DAY 3 (N=1461)	DAY 4 (N=1461)	DAY 5 (N=1461)	DAY 6 (N=1461)	DAY 7 (N=1461)
SYSTEMIC									
Fever (>= 38C)	N	1458	1361	1390	1386	1375	1368	1363	1346
	YES	1 (<1%)	6 (<1%)	13 (1%)	1 (<1%)	4 (<1%)	1 (<1%)	4 (<1%)	4 (<1%)
	NO	1457 (100%)	1355 (100%)	1377 (99%)	1385 (100%)	1371 (100%)	1367 (100%)	1359 (100%)	1342 (100%)
OTHER									
Stayed Home	N	0	1430	1449	1453	1452	1451	1451	1449
	YES	0	12 (1%)	17 (1%)	8 (1%)	3 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	NO	0	1418 (99%)	1432 (99%)	1445 (99%)	1449 (100%)	1450 (100%)	1449 (100%)	1447 (100%)
Analgesic Antipyretics	N	1461	1431	1451	1454	1452	1452	1451	1447
	YES	16 (1%)	68 (5%)	87 (6%)	45 (3%)	19 (1%)	18 (1%)	16 (1%)	13 (1%)
	NO	1445 (99%)	1363 (95%)	1364 (94%)	1409 (97%)	1433 (99%)	1434 (99%)	1435 (99%)	1434 (99%)
Temperature (C)	N	1458	1361	1390	1386	1375	1368	1363	1346
	<38 C	1457 (100%)	1355 (100%)	1377 (99%)	1385 (100%)	1371 (100%)	1367 (100%)	1359 (100%)	1342 (100%)
	38 - 38.9 C	1 (<1%)	5 (<1%)	11 (1%)	1 (<1%)	3 (<1%)	0	4 (<1%)	4 (<1%)
	39.0 - 39.9 C	0	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	1 (<1%)	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total ACWY

Reaction		Number (%) of Subjects							
		30M (N=6185)	6HR (N=6185)	DAY 2 (N=6185)	DAY 3 (N=6185)	DAY 4 (N=6185)	DAY 5 (N=6185)	DAY 6 (N=6185)	DAY 7 (N=6185)
INJECTION SITE									
Pain	N	6175	6057	6086	6090	6084	6082	6082	6076
	ANY	873 (14%)	902 (15%)	518 (9%)	156 (3%)	38 (1%)	20 (<1%)	9 (<1%)	8 (<1%)
	MILD	749 (12%)	735 (12%)	430 (7%)	134 (2%)	31 (1%)	18 (<1%)	7 (<1%)	5 (<1%)
	MODERATE	114 (2%)	156 (3%)	76 (1%)	19 (<1%)	6 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	10 (<1%)	11 (<1%)	12 (<1%)	3 (<1%)	1 (<1%)	0	0	1 (<1%)
Erythema (mm)	N	6176	6052	6080	6082	6080	6079	6078	6071
	ANY	377 (6%)	205 (3%)	203 (3%)	90 (1%)	21 (<1%)	12 (<1%)	12 (<1%)	6 (<1%)
	>0 - 25 mm	366 (6%)	191 (3%)	152 (3%)	56 (1%)	13 (<1%)	7 (<1%)	8 (<1%)	5 (<1%)
	>25 - 50 mm	11 (<1%)	7 (<1%)	34 (1%)	23 (<1%)	6 (<1%)	5 (<1%)	2 (<1%)	0
	> 50 mm	0	7 (<1%)	17 (<1%)	11 (<1%)	2 (<1%)	0	2 (<1%)	1 (<1%)
Induration (mm)	N	6176	6052	6080	6082	6079	6079	6077	6069
	ANY	203 (3%)	197 (3%)	243 (4%)	88 (1%)	20 (<1%)	11 (<1%)	10 (<1%)	3 (<1%)
	>0 - 25 mm	199 (3%)	170 (3%)	182 (3%)	51 (1%)	16 (<1%)	8 (<1%)	9 (<1%)	1 (<1%)
	>25 - 50 mm	3 (<1%)	18 (<1%)	40 (1%)	25 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	> 50 mm	1 (<1%)	9 (<1%)	21 (<1%)	12 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
SYSTEMIC									
Chills	N	6178	6062	6091	6092	6089	6090	6090	6083
	ANY	45 (1%)	139 (2%)	183 (3%)	64 (1%)	41 (1%)	30 (<1%)	22 (<1%)	21 (<1%)
	MILD	37 (1%)	106 (2%)	110 (2%)	50 (1%)	30 (<1%)	19 (<1%)	14 (<1%)	12 (<1%)
	MODERATE	6 (<1%)	26 (<1%)	55 (1%)	10 (<1%)	8 (<1%)	10 (<1%)	7 (<1%)	8 (<1%)
	SEVERE	2 (<1%)	7 (<1%)	18 (<1%)	4 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Nausea	N	6178	6063	6092	6093	6090	6091	6091	6084
	ANY	50 (1%)	169 (3%)	192 (3%)	73 (1%)	52 (1%)	40 (1%)	28 (<1%)	21 (<1%)
	MILD	42 (1%)	143 (2%)	137 (2%)	49 (1%)	37 (1%)	27 (<1%)	22 (<1%)	13 (<1%)
	MODERATE	6 (<1%)	24 (<1%)	44 (1%)	18 (<1%)	13 (<1%)	9 (<1%)	2 (<1%)	6 (<1%)
	SEVERE	2 (<1%)	2 (<1%)	11 (<1%)	6 (<1%)	2 (<1%)	4 (<1%)	4 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total ACWY

Reaction		30M (N=6185)	6HR (N=6185)	DAY 2 (N=6185)	DAY 3 (N=6185)	DAY 4 (N=6185)	DAY 5 (N=6185)	DAY 6 (N=6185)	DAY 7 (N=6185)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	6178	6062	6091	6092	6089	6090	6090	6083
	ANY	77 (1%)	261 (4%)	349 (6%)	128 (2%)	48 (1%)	35 (1%)	36 (1%)	27 (<1%)
	MILD	65 (1%)	204 (3%)	220 (4%)	83 (1%)	31 (1%)	22 (<1%)	23 (<1%)	16 (<1%)
	MODERATE	10 (<1%)	43 (1%)	103 (2%)	34 (1%)	13 (<1%)	10 (<1%)	9 (<1%)	10 (<1%)
	SEVERE	2 (<1%)	14 (<1%)	26 (<1%)	11 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	1 (<1%)
Myalgia	N	6178	6063	6091	6092	6089	6090	6090	6083
	ANY	119 (2%)	407 (7%)	361 (6%)	127 (2%)	34 (1%)	38 (1%)	25 (<1%)	19 (<1%)
	MILD	95 (2%)	306 (5%)	248 (4%)	93 (2%)	28 (<1%)	31 (1%)	15 (<1%)	13 (<1%)
	MODERATE	18 (<1%)	80 (1%)	86 (1%)	27 (<1%)	5 (<1%)	7 (<1%)	6 (<1%)	6 (<1%)
	SEVERE	6 (<1%)	21 (<1%)	27 (<1%)	7 (<1%)	1 (<1%)	0	4 (<1%)	0
Arthralgia	N	6178	6061	6090	6092	6089	6090	6090	6083
	ANY	45 (1%)	165 (3%)	196 (3%)	79 (1%)	26 (<1%)	30 (<1%)	23 (<1%)	16 (<1%)
	MILD	38 (1%)	116 (2%)	140 (2%)	63 (1%)	17 (<1%)	20 (<1%)	16 (<1%)	12 (<1%)
	MODERATE	5 (<1%)	38 (1%)	39 (1%)	11 (<1%)	8 (<1%)	9 (<1%)	6 (<1%)	3 (<1%)
	SEVERE	2 (<1%)	11 (<1%)	17 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Headache	N	6178	6062	6091	6092	6089	6090	6089	6084
	ANY	247 (4%)	583 (10%)	515 (8%)	205 (3%)	136 (2%)	82 (1%)	75 (1%)	38 (1%)
	MILD	203 (3%)	447 (7%)	353 (6%)	142 (2%)	98 (2%)	57 (1%)	54 (1%)	27 (<1%)
	MODERATE	33 (1%)	108 (2%)	120 (2%)	51 (1%)	26 (<1%)	21 (<1%)	14 (<1%)	10 (<1%)
	SEVERE	11 (<1%)	28 (<1%)	42 (1%)	12 (<1%)	12 (<1%)	4 (<1%)	7 (<1%)	1 (<1%)
Rash	N	5310	5197	5226	5227	5222	5223	5223	5217
	ANY	7 (<1%)	28 (1%)	37 (1%)	34 (1%)	23 (<1%)	14 (<1%)	10 (<1%)	7 (<1%)
	OTHER	2 (<1%)	9 (<1%)	11 (<1%)	14 (<1%)	5 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)
	URTICARIAL	5 (<1%)	19 (<1%)	26 (<1%)	20 (<1%)	18 (<1%)	12 (<1%)	7 (<1%)	5 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total ACWY

Reaction		Number (%) of Subjects							
		30M (N=6185)	6HR (N=6185)	DAY 2 (N=6185)	DAY 3 (N=6185)	DAY 4 (N=6185)	DAY 5 (N=6185)	DAY 6 (N=6185)	DAY 7 (N=6185)
SYSTEMIC									
Fever (>= 38C)	N	6164	5863	5906	5897	5863	5855	5846	5784
	YES	8 (<1%)	24 (<1%)	60 (1%)	23 (<1%)	13 (<1%)	11 (<1%)	11 (<1%)	11 (<1%)
	NO	6156 (100%)	5839 (100%)	5846 (99%)	5874 (100%)	5850 (100%)	5844 (100%)	5835 (100%)	5773 (100%)
OTHER									
Stayed Home	N	0	6057	6077	6082	6079	6076	6078	6070
	YES	0	87 (1%)	106 (2%)	35 (1%)	18 (<1%)	6 (<1%)	10 (<1%)	6 (<1%)
	NO	0	5970 (99%)	5971 (98%)	6047 (99%)	6061 (100%)	6070 (100%)	6068 (100%)	6064 (100%)
Analgesic Antipyretics	N	6177	6058	6080	6082	6080	6077	6076	6067
	YES	36 (1%)	251 (4%)	388 (6%)	140 (2%)	87 (1%)	62 (1%)	56 (1%)	46 (1%)
	NO	6141 (99%)	5807 (96%)	5692 (94%)	5942 (98%)	5993 (99%)	6015 (99%)	6020 (99%)	6021 (99%)
Temperature (C)	N	6164	5863	5906	5897	5863	5855	5846	5784
	<38 C	6156 (100%)	5839 (100%)	5846 (99%)	5874 (100%)	5850 (100%)	5844 (100%)	5835 (100%)	5773 (100%)
	38 - 38.9 C	8 (<1%)	20 (<1%)	51 (1%)	19 (<1%)	10 (<1%)	8 (<1%)	10 (<1%)	8 (<1%)
	39.0 - 39.9 C	0	4 (<1%)	8 (<1%)	3 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)
	>= 40 C	0	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total Menactra

Reaction		30M (N=1757)	6HR (N=1757)	DAY 2 (N=1757)	DAY 3 (N=1757)	DAY 4 (N=1757)	DAY 5 (N=1757)	DAY 6 (N=1757)	DAY 7 (N=1757)
		Number (%) of Subjects							
INJECTION SITE									
Pain	N	1756	1719	1740	1737	1739	1740	1739	1736
	ANY	299 (17%)	294 (17%)	180 (10%)	33 (2%)	5 (<1%)	3 (<1%)	2 (<1%)	0
	MILD	253 (14%)	259 (15%)	147 (8%)	29 (2%)	5 (<1%)	3 (<1%)	2 (<1%)	0
	MODERATE	45 (3%)	33 (2%)	27 (2%)	2 (<1%)	0	0	0	0
	SEVERE	1 (<1%)	2 (<1%)	6 (<1%)	2 (<1%)	0	0	0	0
Erythema (mm)	N	1757	1716	1738	1735	1737	1738	1737	1735
	ANY	92 (5%)	41 (2%)	68 (4%)	23 (1%)	1 (<1%)	4 (<1%)	2 (<1%)	0
	>0 - 25 mm	91 (5%)	37 (2%)	54 (3%)	17 (1%)	1 (<1%)	4 (<1%)	1 (<1%)	0
	>25 - 50 mm	1 (<1%)	3 (<1%)	11 (1%)	1 (<1%)	0	0	1 (<1%)	0
	> 50 mm	0	1 (<1%)	3 (<1%)	5 (<1%)	0	0	0	0
Induration (mm)	N	1757	1717	1739	1736	1738	1739	1738	1736
	ANY	65 (4%)	47 (3%)	68 (4%)	20 (1%)	1 (<1%)	2 (<1%)	0	0
	>0 - 25 mm	63 (4%)	41 (2%)	55 (3%)	15 (1%)	1 (<1%)	2 (<1%)	0	0
	>25 - 50 mm	2 (<1%)	4 (<1%)	9 (1%)	5 (<1%)	0	0	0	0
	> 50 mm	0	2 (<1%)	4 (<1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	10 (1%)	24 (1%)	41 (2%)	13 (1%)	14 (1%)	9 (1%)	7 (<1%)	2 (<1%)
	MILD	9 (1%)	18 (1%)	31 (2%)	9 (1%)	10 (1%)	8 (<1%)	6 (<1%)	2 (<1%)
	MODERATE	1 (<1%)	6 (<1%)	7 (<1%)	3 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	0	3 (<1%)	1 (<1%)	0	0	0	0
Nausea	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	14 (1%)	31 (2%)	43 (2%)	18 (1%)	13 (1%)	10 (1%)	7 (<1%)	6 (<1%)
	MILD	10 (1%)	27 (2%)	34 (2%)	13 (1%)	7 (<1%)	5 (<1%)	7 (<1%)	3 (<1%)
	MODERATE	4 (<1%)	3 (<1%)	8 (<1%)	4 (<1%)	5 (<1%)	4 (<1%)	0	2 (<1%)
	SEVERE	0	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total Menactra

Reaction		30M (N=1757)	6HR (N=1757)	DAY 2 (N=1757)	DAY 3 (N=1757)	DAY 4 (N=1757)	DAY 5 (N=1757)	DAY 6 (N=1757)	DAY 7 (N=1757)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	37 (2%)	78 (5%)	77 (4%)	43 (2%)	16 (1%)	16 (1%)	12 (1%)	6 (<1%)
	MILD	34 (2%)	59 (3%)	52 (3%)	26 (1%)	10 (1%)	13 (1%)	9 (1%)	4 (<1%)
	MODERATE	3 (<1%)	18 (1%)	20 (1%)	14 (1%)	3 (<1%)	3 (<1%)	3 (<1%)	2 (<1%)
	SEVERE	0	1 (<1%)	5 (<1%)	3 (<1%)	3 (<1%)	0	0	0
Myalgia	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	24 (1%)	81 (5%)	89 (5%)	32 (2%)	18 (1%)	16 (1%)	12 (1%)	8 (<1%)
	MILD	23 (1%)	68 (4%)	61 (4%)	17 (1%)	13 (1%)	11 (1%)	9 (1%)	5 (<1%)
	MODERATE	1 (<1%)	12 (1%)	22 (1%)	14 (1%)	4 (<1%)	4 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	0	1 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Arthralgia	N	1757	1719	1740	1738	1739	1741	1740	1738
	ANY	10 (1%)	25 (1%)	45 (3%)	19 (1%)	12 (1%)	10 (1%)	1 (<1%)	8 (<1%)
	MILD	10 (1%)	19 (1%)	33 (2%)	10 (1%)	9 (1%)	8 (<1%)	1 (<1%)	8 (<1%)
	MODERATE	0	6 (<1%)	10 (1%)	7 (<1%)	2 (<1%)	2 (<1%)	0	0
	SEVERE	0	0	2 (<1%)	2 (<1%)	1 (<1%)	0	0	0
Headache	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	62 (4%)	130 (8%)	124 (7%)	76 (4%)	42 (2%)	19 (1%)	22 (1%)	16 (1%)
	MILD	52 (3%)	96 (6%)	93 (5%)	52 (3%)	26 (1%)	12 (1%)	20 (1%)	12 (1%)
	MODERATE	9 (1%)	25 (1%)	25 (1%)	19 (1%)	12 (1%)	6 (<1%)	2 (<1%)	4 (<1%)
	SEVERE	1 (<1%)	9 (1%)	6 (<1%)	5 (<1%)	4 (<1%)	1 (<1%)	0	0
Rash	N	1757	1719	1741	1738	1739	1741	1740	1738
	ANY	0	8 (<1%)	12 (1%)	12 (1%)	3 (<1%)	0	4 (<1%)	3 (<1%)
	OTHER	0	1 (<1%)	4 (<1%)	6 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
	URTICARIAL	0	7 (<1%)	8 (<1%)	6 (<1%)	2 (<1%)	0	2 (<1%)	1 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 26

Summary of Time of First Onset of Reactogenicity, Comparing Total MenACWY[1] across Age Groups

Group: Total Menactra

Reaction		Number (%) of Subjects							
		30M (N=1757)	6HR (N=1757)	DAY 2 (N=1757)	DAY 3 (N=1757)	DAY 4 (N=1757)	DAY 5 (N=1757)	DAY 6 (N=1757)	DAY 7 (N=1757)
SYSTEMIC									
Fever (>= 38C)	N	1753	1624	1647	1634	1629	1627	1619	1602
	YES	1 (<1%)	5 (<1%)	9 (1%)	11 (1%)	4 (<1%)	4 (<1%)	0	3 (<1%)
	NO	1752 (100%)	1619 (100%)	1638 (99%)	1623 (99%)	1625 (100%)	1623 (100%)	1619 (100%)	1599 (100%)
OTHER									
Stayed Home	N	0	1717	1741	1737	1741	1742	1739	1739
	YES	0	16 (1%)	17 (1%)	10 (1%)	7 (<1%)	8 (<1%)	2 (<1%)	3 (<1%)
	NO	0	1701 (99%)	1724 (99%)	1727 (99%)	1734 (100%)	1734 (100%)	1737 (100%)	1736 (100%)
Analgesic Antipyretics	N	1755	1717	1738	1735	1739	1740	1739	1738
	YES	10 (1%)	88 (5%)	95 (5%)	61 (4%)	27 (2%)	20 (1%)	14 (1%)	11 (1%)
	NO	1745 (99%)	1629 (95%)	1643 (95%)	1674 (96%)	1712 (98%)	1720 (99%)	1725 (99%)	1727 (99%)
Temperature (C)	N	1753	1624	1647	1634	1629	1627	1619	1602
	<38 C	1752 (100%)	1619 (100%)	1638 (99%)	1623 (99%)	1625 (100%)	1623 (100%)	1619 (100%)	1599 (100%)
	38 - 38.9 C	1 (<1%)	5 (<1%)	6 (<1%)	7 (<1%)	3 (<1%)	3 (<1%)	0	2 (<1%)
	39.0 - 39.9 C	0	0	2 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
	>= 40 C	0	0	1 (<1%)	1 (<1%)	0	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY.SAS(WARTERO) 10JUL08, 08:39 SAS.9.1 - PINJONSET_ACWY

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
INJECTION SITE									
Pain	N	151	150	150	150	149	150	149	149
	ANY	26 (17%)	31 (21%)	21 (14%)	3 (2%)	0	0	0	0
	MILD	23 (15%)	29 (19%)	19 (13%)	3 (2%)	0	0	0	0
	MODERATE	3 (2%)	2 (1%)	2 (1%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	151	148	148	148	147	148	148	147
	ANY	48 (32%)	2 (1%)	5 (3%)	2 (1%)	0	0	0	0
	>0 - 25 mm	45 (30%)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0
	>25 - 50 mm	3 (2%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	1 (1%)	3 (2%)	1 (1%)	0	0	0	0
Induration (mm)	N	151	149	149	149	148	149	149	148
	ANY	22 (15%)	3 (2%)	8 (5%)	1 (1%)	0	0	0	0
	>0 - 25 mm	20 (13%)	3 (2%)	4 (3%)	0	0	0	0	0
	>25 - 50 mm	2 (1%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	0	3 (2%)	1 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	12 (8%)	1 (1%)	5 (3%)	0	1 (1%)	2 (1%)
	MILD	0	2 (1%)	8 (5%)	1 (1%)	4 (3%)	0	1 (1%)	1 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	2 (1%)	0	0	0	0	0
Nausea	N	151	150	150	150	149	150	150	149
	ANY	2 (1%)	5 (3%)	8 (5%)	1 (1%)	2 (1%)	0	0	4 (3%)
	MILD	2 (1%)	4 (3%)	6 (4%)	0	1 (1%)	0	0	2 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	0	1 (1%)	0	0	0	1 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
SYSTEMIC									
Malaise	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	0	13 (9%)	1 (1%)	2 (1%)	0	4 (3%)	2 (1%)
	MILD	1 (1%)	0	9 (6%)	0	1 (1%)	0	2 (1%)	1 (1%)
	MODERATE	0	0	2 (1%)	0	1 (1%)	0	2 (1%)	1 (1%)
	SEVERE	0	0	2 (1%)	1 (1%)	0	0	0	0
Myalgia	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	14 (9%)	7 (5%)	8 (5%)	3 (2%)	1 (1%)	1 (1%)	0
	MILD	1 (1%)	12 (8%)	3 (2%)	8 (5%)	2 (1%)	1 (1%)	1 (1%)	0
	MODERATE	0	2 (1%)	3 (2%)	0	1 (1%)	0	0	0
	SEVERE	0	0	1 (1%)	0	0	0	0	0
Arthralgia	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MILD	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MODERATE	0	0	0	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	151	150	150	150	149	150	150	149
	ANY	11 (7%)	9 (6%)	24 (16%)	3 (2%)	3 (2%)	3 (2%)	6 (4%)	3 (2%)
	MILD	11 (7%)	9 (6%)	16 (11%)	1 (1%)	2 (1%)	3 (2%)	5 (3%)	2 (1%)
	MODERATE	0	0	5 (3%)	1 (1%)	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	3 (2%)	1 (1%)	0	0	1 (1%)	0
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	151	149	149	146	144	146	147	148
	YES	0	0	0	0	0	0	0	1 (1%)
	NO	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
OTHER									
Stayed Home	N	0	150	149	149	148	149	148	148
	YES	0	0	4 (3%)	1 (1%)	0	0	1 (1%)	0
	NO	0	150 (100%)	145 (97%)	148 (99%)	148 (100%)	149 (100%)	147 (99%)	148 (100%)
Analgesic Antipyretics	N	151	150	149	149	148	149	148	148
	YES	2 (1%)	7 (5%)	15 (10%)	3 (2%)	4 (3%)	2 (1%)	3 (2%)	3 (2%)
	NO	149 (99%)	143 (95%)	134 (90%)	146 (98%)	144 (97%)	147 (99%)	145 (98%)	145 (98%)
Temperature (C)	N	151	149	149	146	144	146	147	148
	<38 C	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)
	38 - 38.9 C	0	0	0	0	0	0	0	1 (1%)
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=209)	6HR (N=209)	DAY 2 (N=209)	DAY 3 (N=209)	DAY 4 (N=209)	DAY 5 (N=209)	DAY 6 (N=209)	DAY 7 (N=209)
INJECTION SITE									
Pain	N	209	209	209	208	209	209	207	209
	ANY	19 (9%)	80 (38%)	13 (6%)	0	1 (<1%)	1 (<1%)	0	0
	MILD	18 (9%)	66 (32%)	13 (6%)	0	0	0	0	0
	MODERATE	1 (<1%)	13 (6%)	0	0	1 (<1%)	1 (<1%)	0	0
	SEVERE	0	1 (<1%)	0	0	0	0	0	0
Erythema (mm)	N	209	209	209	208	209	209	207	209
	ANY	27 (13%)	9 (4%)	3 (1%)	0	0	0	0	0
	>0 - 25 mm	27 (13%)	9 (4%)	2 (1%)	0	0	0	0	0
	>25 - 50 mm	0	0	1 (<1%)	0	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	209	209	209	208	209	209	207	209
	ANY	16 (8%)	5 (2%)	2 (1%)	0	0	0	0	0
	>0 - 25 mm	16 (8%)	5 (2%)	2 (1%)	0	0	0	0	0
	>25 - 50 mm	0	0	0	0	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
SYSTEMIC									
Chills	N	209	209	209	208	209	209	207	209
	ANY	2 (1%)	3 (1%)	3 (1%)	5 (2%)	1 (<1%)	1 (<1%)	0	1 (<1%)
	MILD	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	1 (<1%)	0	0	0	0	0	0	1 (<1%)
	SEVERE	0	0	0	0	0	0	0	0
Nausea	N	209	209	209	208	209	209	207	209
	ANY	1 (<1%)	4 (2%)	4 (2%)	2 (1%)	4 (2%)	1 (<1%)	1 (<1%)	3 (1%)
	MILD	1 (<1%)	3 (1%)	3 (1%)	0	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)
	MODERATE	0	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)
	SEVERE	0	0	0	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=209)	6HR (N=209)	DAY 2 (N=209)	DAY 3 (N=209)	DAY 4 (N=209)	DAY 5 (N=209)	DAY 6 (N=209)	DAY 7 (N=209)
SYSTEMIC									
Malaise	N	209	209	209	208	209	209	207	209
	ANY	2 (1%)	3 (1%)	6 (3%)	3 (1%)	1 (<1%)	2 (1%)	1 (<1%)	3 (1%)
	MILD	2 (1%)	3 (1%)	5 (2%)	2 (1%)	1 (<1%)	2 (1%)	0	1 (<1%)
	MODERATE	0	0	1 (<1%)	1 (<1%)	0	0	0	2 (1%)
	SEVERE	0	0	0	0	0	0	1 (<1%)	0
Myalgia	N	209	209	209	208	209	209	207	209
	ANY	2 (1%)	11 (5%)	4 (2%)	3 (1%)	3 (1%)	4 (2%)	2 (1%)	1 (<1%)
	MILD	1 (<1%)	7 (3%)	4 (2%)	3 (1%)	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)
	MODERATE	1 (<1%)	4 (2%)	0	0	1 (<1%)	2 (1%)	1 (<1%)	0
	SEVERE	0	0	0	0	0	0	0	0
Arthralgia	N	209	209	209	208	209	209	207	209
	ANY	0	0	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)	0	0
	MILD	0	0	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	0	0	1 (<1%)	0	0	1 (<1%)	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	209	209	209	208	208	208	207	209
	ANY	17 (8%)	16 (8%)	15 (7%)	15 (7%)	7 (3%)	3 (1%)	6 (3%)	3 (1%)
	MILD	15 (7%)	15 (7%)	12 (6%)	7 (3%)	6 (3%)	1 (<1%)	5 (2%)	0
	MODERATE	2 (1%)	1 (<1%)	3 (1%)	5 (2%)	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
	SEVERE	0	0	0	3 (1%)	0	0	0	2 (1%)
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	209	205	207	207	207	206	205	204
	YES	0	0	0	0	1 (<1%)	0	1 (<1%)	2 (1%)
	NO	209 (100%)	205 (100%)	207 (100%)	207 (100%)	206 (100%)	206 (100%)	204 (100%)	202 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=209)	6HR (N=209)	DAY 2 (N=209)	DAY 3 (N=209)	DAY 4 (N=209)	DAY 5 (N=209)	DAY 6 (N=209)	DAY 7 (N=209)
OTHER									
Stayed Home	N	0	209	209	208	209	209	207	209
	YES	0	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)
	NO	0	209 (100%)	208 (100%)	207 (100%)	209 (100%)	208 (100%)	207 (100%)	208 (100%)
Analgesic Antipyretics	N	209	208	208	207	208	208	206	208
	YES	2 (1%)	11 (5%)	15 (7%)	8 (4%)	7 (3%)	5 (2%)	4 (2%)	7 (3%)
	NO	207 (99%)	197 (95%)	193 (93%)	199 (96%)	201 (97%)	203 (98%)	202 (98%)	201 (97%)
Temperature (C)	N	209	205	207	207	207	206	205	204
	<38 C	209 (100%)	205 (100%)	207 (100%)	207 (100%)	206 (100%)	206 (100%)	204 (100%)	202 (99%)
	38 - 38.9 C	0	0	0	0	1 (<1%)	0	1 (<1%)	2 (1%)
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
INJECTION SITE									
Pain	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	67 (19%)	28 (8%)	10 (3%)	1 (<1%)	1 (<1%)	0	0
	MILD	6 (2%)	51 (14%)	24 (7%)	8 (2%)	0	1 (<1%)	0	0
	MODERATE	3 (1%)	12 (3%)	3 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	0	4 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	40 (11%)	11 (3%)	6 (2%)	0	0	0	0
	>0 - 25 mm	9 (3%)	40 (11%)	9 (3%)	3 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	357	357	357	357	357	357	357	357
	ANY	5 (1%)	29 (8%)	17 (5%)	7 (2%)	0	0	0	1 (<1%)
	>0 - 25 mm	5 (1%)	28 (8%)	15 (4%)	4 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	1 (<1%)
	> 50 mm	0	1 (<1%)	0	0	0	0	0	0
SYSTEMIC									
Chills	N	357	357	357	357	357	357	357	357
	ANY	0	21 (6%)	7 (2%)	6 (2%)	3 (1%)	5 (1%)	2 (1%)	3 (1%)
	MILD	0	14 (4%)	5 (1%)	3 (1%)	0	3 (1%)	2 (1%)	3 (1%)
	MODERATE	0	5 (1%)	2 (1%)	2 (1%)	2 (1%)	2 (1%)	0	0
	SEVERE	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0	0
Nausea	N	357	357	357	357	357	357	357	357
	ANY	0	8 (2%)	9 (3%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	3 (1%)
	MILD	0	6 (2%)	7 (2%)	2 (1%)	1 (<1%)	0	2 (1%)	3 (1%)
	MODERATE	0	2 (1%)	2 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	0	0	2 (1%)	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
SYSTEMIC									
Malaise	N	357	357	357	357	357	357	357	357
	ANY	0	24 (7%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)	0	2 (1%)
	MILD	0	17 (5%)	3 (1%)	4 (1%)	2 (1%)	1 (<1%)	0	1 (<1%)
	MODERATE	0	7 (2%)	4 (1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)
	SEVERE	0	0	0	1 (<1%)	0	0	0	0
Myalgia	N	357	357	357	357	357	357	357	357
	ANY	0	46 (13%)	18 (5%)	10 (3%)	2 (1%)	2 (1%)	1 (<1%)	0
	MILD	0	33 (9%)	12 (3%)	7 (2%)	2 (1%)	2 (1%)	0	0
	MODERATE	0	10 (3%)	6 (2%)	2 (1%)	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	0	1 (<1%)	0	0	0	0
Arthralgia	N	357	357	357	357	357	357	357	357
	ANY	0	23 (6%)	8 (2%)	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)	2 (1%)
	MILD	0	15 (4%)	5 (1%)	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
	MODERATE	0	5 (1%)	2 (1%)	0	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Headache	N	357	357	357	357	357	357	357	357
	ANY	3 (1%)	64 (18%)	29 (8%)	10 (3%)	6 (2%)	9 (3%)	4 (1%)	3 (1%)
	MILD	3 (1%)	45 (13%)	21 (6%)	9 (3%)	5 (1%)	6 (2%)	3 (1%)	2 (1%)
	MODERATE	0	13 (4%)	5 (1%)	1 (<1%)	0	3 (1%)	0	0
	SEVERE	0	6 (2%)	3 (1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	357	356	356	357	356	355	355	353
	YES	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	3 (1%)	2 (1%)	0
	NO	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
OTHER									
Stayed Home	N	0	357	357	357	357	357	357	356
	YES	0	1 (<1%)	4 (1%)	3 (1%)	2 (1%)	2 (1%)	0	0
	NO	0	356 (100%)	353 (99%)	354 (99%)	355 (99%)	355 (99%)	357 (100%)	356 (100%)
Analgesic Antipyretics	N	357	357	357	357	357	357	357	356
	YES	0	6 (2%)	8 (2%)	5 (1%)	4 (1%)	3 (1%)	2 (1%)	3 (1%)
	NO	357 (100%)	351 (98%)	349 (98%)	352 (99%)	353 (99%)	354 (99%)	355 (99%)	353 (99%)
Temperature (C)	N	357	356	356	357	356	355	355	353
	<38 C	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)
	38 - 38.9 C	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	0
	39.0 - 39.9 C	0	0	0	0	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=353)	6HR (N=353)	DAY 2 (N=353)	DAY 3 (N=353)	DAY 4 (N=353)	DAY 5 (N=353)	DAY 6 (N=353)	DAY 7 (N=353)
INJECTION SITE									
Pain	N	353	353	353	353	353	353	353	352
	ANY	7 (2%)	209 (59%)	29 (8%)	1 (<1%)	0	0	0	0
	MILD	5 (1%)	142 (40%)	20 (6%)	1 (<1%)	0	0	0	0
	MODERATE	2 (1%)	62 (18%)	8 (2%)	0	0	0	0	0
	SEVERE	0	5 (1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	353	353	353	353	353	353	353	352
	ANY	5 (1%)	63 (18%)	31 (9%)	3 (1%)	1 (<1%)	0	0	0
	>0 - 25 mm	5 (1%)	62 (18%)	23 (7%)	2 (1%)	1 (<1%)	0	0	0
	>25 - 50 mm	0	1 (<1%)	5 (1%)	1 (<1%)	0	0	0	0
	> 50 mm	0	0	3 (1%)	0	0	0	0	0
Induration (mm)	N	353	353	353	353	353	353	353	352
	ANY	1 (<1%)	69 (20%)	42 (12%)	5 (1%)	0	0	1 (<1%)	0
	>0 - 25 mm	1 (<1%)	56 (16%)	29 (8%)	2 (1%)	0	0	1 (<1%)	0
	>25 - 50 mm	0	13 (4%)	11 (3%)	3 (1%)	0	0	0	0
	> 50 mm	0	0	2 (1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	353	353	353	353	353	353	353	352
	ANY	2 (1%)	15 (4%)	18 (5%)	2 (1%)	1 (<1%)	1 (<1%)	2 (1%)	0
	MILD	2 (1%)	13 (4%)	12 (3%)	1 (<1%)	0	1 (<1%)	2 (1%)	0
	MODERATE	0	2 (1%)	3 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	0	0	3 (1%)	0	0	0	0	0
Nausea	N	353	353	353	353	353	353	353	352
	ANY	1 (<1%)	12 (3%)	11 (3%)	4 (1%)	5 (1%)	0	1 (<1%)	1 (<1%)
	MILD	0	9 (3%)	9 (3%)	2 (1%)	3 (1%)	0	1 (<1%)	1 (<1%)
	MODERATE	1 (<1%)	2 (1%)	2 (1%)	1 (<1%)	2 (1%)	0	0	0
	SEVERE	0	1 (<1%)	0	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=353)	6HR (N=353)	DAY 2 (N=353)	DAY 3 (N=353)	DAY 4 (N=353)	DAY 5 (N=353)	DAY 6 (N=353)	DAY 7 (N=353)
SYSTEMIC									
Malaise	N	353	353	353	353	353	353	353	352
	ANY	0	21 (6%)	23 (7%)	3 (1%)	3 (1%)	3 (1%)	4 (1%)	0
	MILD	0	18 (5%)	16 (5%)	3 (1%)	2 (1%)	2 (1%)	4 (1%)	0
	MODERATE	0	3 (1%)	5 (1%)	0	1 (<1%)	1 (<1%)	0	0
	SEVERE	0	0	2 (1%)	0	0	0	0	0
Myalgia	N	353	353	353	353	353	353	353	352
	ANY	3 (1%)	92 (26%)	23 (7%)	6 (2%)	1 (<1%)	2 (1%)	0	0
	MILD	2 (1%)	69 (20%)	14 (4%)	5 (1%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	1 (<1%)	21 (6%)	7 (2%)	1 (<1%)	0	0	0	0
	SEVERE	0	2 (1%)	2 (1%)	0	0	1 (<1%)	0	0
Arthralgia	N	353	353	353	353	353	353	353	352
	ANY	1 (<1%)	43 (12%)	12 (3%)	1 (<1%)	2 (1%)	1 (<1%)	0	0
	MILD	0	34 (10%)	5 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	1 (<1%)	8 (2%)	6 (2%)	0	1 (<1%)	0	0	0
	SEVERE	0	1 (<1%)	1 (<1%)	0	0	0	0	0
Headache	N	353	353	353	353	353	353	353	352
	ANY	6 (2%)	53 (15%)	29 (8%)	6 (2%)	7 (2%)	2 (1%)	4 (1%)	3 (1%)
	MILD	5 (1%)	43 (12%)	20 (6%)	6 (2%)	5 (1%)	2 (1%)	3 (1%)	3 (1%)
	MODERATE	1 (<1%)	6 (2%)	7 (2%)	0	1 (<1%)	0	1 (<1%)	0
	SEVERE	0	4 (1%)	2 (1%)	0	1 (<1%)	0	0	0
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	353	352	353	352	353	349	352	351
	YES	0	2 (1%)	5 (1%)	0	0	0	0	0
	NO	353 (100%)	350 (99%)	348 (99%)	352 (100%)	353 (100%)	349 (100%)	352 (100%)	351 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=353)	6HR (N=353)	DAY 2 (N=353)	DAY 3 (N=353)	DAY 4 (N=353)	DAY 5 (N=353)	DAY 6 (N=353)	DAY 7 (N=353)
OTHER									
Stayed Home	N	0	353	353	353	353	353	353	352
	YES	0	1 (<1%)	10 (3%)	3 (1%)	0	1 (<1%)	0	0
	NO	0	352 (100%)	343 (97%)	350 (99%)	353 (100%)	352 (100%)	353 (100%)	352 (100%)
Analgesic Antipyretics	N	353	353	353	353	353	353	353	352
	YES	0	10 (3%)	17 (5%)	8 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)
	NO	353 (100%)	343 (97%)	336 (95%)	345 (98%)	352 (100%)	353 (100%)	352 (100%)	351 (100%)
Temperature (C)	N	353	352	353	352	353	349	352	351
	<38 C	353 (100%)	350 (99%)	348 (99%)	352 (100%)	353 (100%)	349 (100%)	352 (100%)	351 (100%)
	38 - 38.9 C	0	2 (1%)	5 (1%)	0	0	0	0	0
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
INJECTION SITE									
Pain	N	1622	1607	1610	1610	1609	1607	1609	1607
	ANY	212 (13%)	296 (18%)	145 (9%)	44 (3%)	9 (1%)	7 (<1%)	0	1 (<1%)
	MILD	197 (12%)	260 (16%)	120 (7%)	43 (3%)	6 (<1%)	7 (<1%)	0	1 (<1%)
	MODERATE	14 (1%)	35 (2%)	22 (1%)	1 (<1%)	2 (<1%)	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	3 (<1%)	0	1 (<1%)	0	0	0
Erythema (mm)	N	1623	1607	1611	1611	1610	1610	1609	1608
	ANY	64 (4%)	57 (4%)	80 (5%)	34 (2%)	6 (<1%)	4 (<1%)	2 (<1%)	0
	>0 - 25 mm	61 (4%)	53 (3%)	56 (3%)	20 (1%)	4 (<1%)	3 (<1%)	2 (<1%)	0
	>25 - 50 mm	3 (<1%)	1 (<1%)	13 (1%)	9 (1%)	2 (<1%)	1 (<1%)	0	0
	> 50 mm	0	3 (<1%)	11 (1%)	5 (<1%)	0	0	0	0
Induration (mm)	N	1623	1607	1611	1610	1610	1610	1609	1608
	ANY	34 (2%)	55 (3%)	76 (5%)	26 (2%)	1 (<1%)	2 (<1%)	2 (<1%)	0
	>0 - 25 mm	34 (2%)	45 (3%)	53 (3%)	12 (1%)	0	2 (<1%)	2 (<1%)	0
	>25 - 50 mm	0	7 (<1%)	13 (1%)	9 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	3 (<1%)	10 (1%)	5 (<1%)	0	0	0	0
SYSTEMIC									
Chills	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	18 (1%)	27 (2%)	49 (3%)	13 (1%)	6 (<1%)	9 (1%)	1 (<1%)	4 (<1%)
	MILD	16 (1%)	24 (1%)	31 (2%)	10 (1%)	6 (<1%)	4 (<1%)	1 (<1%)	0
	MODERATE	2 (<1%)	1 (<1%)	15 (1%)	3 (<1%)	0	5 (<1%)	0	3 (<1%)
	SEVERE	0	2 (<1%)	3 (<1%)	0	0	0	0	1 (<1%)
Nausea	N	1625	1610	1613	1613	1612	1612	1612	1610
	ANY	14 (1%)	41 (3%)	62 (4%)	26 (2%)	16 (1%)	11 (1%)	9 (1%)	8 (<1%)
	MILD	12 (1%)	36 (2%)	42 (3%)	16 (1%)	12 (1%)	7 (<1%)	6 (<1%)	4 (<1%)
	MODERATE	2 (<1%)	5 (<1%)	17 (1%)	7 (<1%)	4 (<1%)	4 (<1%)	1 (<1%)	4 (<1%)
	SEVERE	0	0	3 (<1%)	3 (<1%)	0	0	2 (<1%)	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
SYSTEMIC									
Malaise	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	17 (1%)	33 (2%)	71 (4%)	26 (2%)	8 (<1%)	7 (<1%)	9 (1%)	6 (<1%)
	MILD	15 (1%)	25 (2%)	39 (2%)	16 (1%)	7 (<1%)	4 (<1%)	6 (<1%)	3 (<1%)
	MODERATE	2 (<1%)	8 (<1%)	23 (1%)	9 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	0	0	9 (1%)	1 (<1%)	0	1 (<1%)	0	0
Myalgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	31 (2%)	112 (7%)	102 (6%)	31 (2%)	6 (<1%)	15 (1%)	6 (<1%)	7 (<1%)
	MILD	28 (2%)	95 (6%)	74 (5%)	24 (1%)	6 (<1%)	14 (1%)	2 (<1%)	4 (<1%)
	MODERATE	1 (<1%)	14 (1%)	20 (1%)	7 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	2 (<1%)	3 (<1%)	8 (<1%)	0	0	0	1 (<1%)	0
Arthralgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	9 (1%)	25 (2%)	53 (3%)	20 (1%)	7 (<1%)	13 (1%)	4 (<1%)	6 (<1%)
	MILD	9 (1%)	22 (1%)	41 (3%)	19 (1%)	5 (<1%)	9 (1%)	2 (<1%)	5 (<1%)
	MODERATE	0	2 (<1%)	8 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	4 (<1%)	0	0	1 (<1%)	0	0
Headache	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	63 (4%)	131 (8%)	134 (8%)	44 (3%)	41 (3%)	27 (2%)	26 (2%)	12 (1%)
	MILD	57 (4%)	102 (6%)	99 (6%)	31 (2%)	33 (2%)	21 (1%)	20 (1%)	8 (<1%)
	MODERATE	5 (<1%)	25 (2%)	29 (2%)	12 (1%)	7 (<1%)	5 (<1%)	3 (<1%)	4 (<1%)
	SEVERE	1 (<1%)	4 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
Rash	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	0	4 (<1%)	15 (1%)	9 (1%)	4 (<1%)	6 (<1%)	3 (<1%)	3 (<1%)
	OTHER	0	3 (<1%)	4 (<1%)	7 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	URTICARIAL	0	1 (<1%)	11 (1%)	2 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)
Fever (>= 38C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	YES	0	4 (<1%)	11 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
	NO	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
OTHER									
Stayed Home	N	0	1609	1610	1610	1610	1608	1610	1609
	YES	0	7 (<1%)	25 (2%)	6 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)
	NO	0	1602 (100%)	1585 (98%)	1604 (100%)	1606 (100%)	1605 (100%)	1606 (100%)	1606 (100%)
Analgesic Antipyretics	N	1625	1610	1612	1611	1612	1610	1611	1610
	YES	4 (<1%)	75 (5%)	113 (7%)	29 (2%)	24 (1%)	18 (1%)	17 (1%)	13 (1%)
	NO	1621 (100%)	1535 (95%)	1499 (93%)	1582 (98%)	1588 (99%)	1592 (99%)	1594 (99%)	1597 (99%)
Temperature (C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	<38 C	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)
	38 - 38.9 C	0	3 (<1%)	9 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	1 (<1%)	2 (<1%)	0	0	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
INJECTION SITE									
Pain	N	538	531	531	530	531	531	531	531
	ANY	94 (17%)	116 (22%)	69 (13%)	6 (1%)	1 (<1%)	1 (<1%)	0	0
	MILD	83 (15%)	106 (20%)	56 (11%)	5 (1%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	11 (2%)	10 (2%)	12 (2%)	0	0	0	0	0
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	539	531	531	530	531	531	531	531
	ANY	22 (4%)	14 (3%)	39 (7%)	9 (2%)	0	0	1 (<1%)	0
	>0 - 25 mm	22 (4%)	13 (2%)	32 (6%)	7 (1%)	0	0	1 (<1%)	0
	>25 - 50 mm	0	1 (<1%)	6 (1%)	0	0	0	0	0
	> 50 mm	0	0	1 (<1%)	2 (<1%)	0	0	0	0
Induration (mm)	N	539	531	531	530	531	531	531	531
	ANY	3 (1%)	22 (4%)	27 (5%)	7 (1%)	0	0	0	0
	>0 - 25 mm	3 (1%)	20 (4%)	21 (4%)	7 (1%)	0	0	0	0
	>25 - 50 mm	0	1 (<1%)	5 (1%)	0	0	0	0	0
	> 50 mm	0	1 (<1%)	1 (<1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	539	531	531	530	531	531	531	531
	ANY	6 (1%)	6 (1%)	14 (3%)	3 (1%)	4 (1%)	2 (<1%)	3 (1%)	0
	MILD	5 (1%)	6 (1%)	12 (2%)	2 (<1%)	4 (1%)	2 (<1%)	3 (1%)	0
	MODERATE	1 (<1%)	0	2 (<1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Nausea	N	539	531	531	530	531	531	531	531
	ANY	4 (1%)	9 (2%)	21 (4%)	6 (1%)	3 (1%)	2 (<1%)	2 (<1%)	0
	MILD	2 (<1%)	9 (2%)	16 (3%)	3 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	0
	MODERATE	2 (<1%)	0	4 (1%)	3 (1%)	1 (<1%)	1 (<1%)	0	0
	SEVERE	0	0	1 (<1%)	0	1 (<1%)	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
SYSTEMIC									
Malaise	N	539	531	531	530	531	531	531	531
	ANY	12 (2%)	15 (3%)	23 (4%)	8 (2%)	3 (1%)	2 (<1%)	1 (<1%)	1 (<1%)
	MILD	12 (2%)	12 (2%)	14 (3%)	5 (1%)	1 (<1%)	2 (<1%)	1 (<1%)	0
	MODERATE	0	3 (1%)	7 (1%)	3 (1%)	1 (<1%)	0	0	1 (<1%)
	SEVERE	0	0	2 (<1%)	0	1 (<1%)	0	0	0
Myalgia	N	539	531	531	530	531	531	531	531
	ANY	12 (2%)	33 (6%)	33 (6%)	6 (1%)	5 (1%)	3 (1%)	3 (1%)	4 (1%)
	MILD	11 (2%)	30 (6%)	23 (4%)	5 (1%)	4 (1%)	3 (1%)	3 (1%)	2 (<1%)
	MODERATE	1 (<1%)	3 (1%)	8 (2%)	1 (<1%)	1 (<1%)	0	0	2 (<1%)
	SEVERE	0	0	2 (<1%)	0	0	0	0	0
Arthralgia	N	539	531	531	530	531	531	531	531
	ANY	3 (1%)	10 (2%)	11 (2%)	2 (<1%)	2 (<1%)	3 (1%)	0	3 (1%)
	MILD	3 (1%)	9 (2%)	10 (2%)	2 (<1%)	2 (<1%)	2 (<1%)	0	3 (1%)
	MODERATE	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	539	531	531	530	531	531	531	531
	ANY	23 (4%)	35 (7%)	43 (8%)	23 (4%)	15 (3%)	5 (1%)	4 (1%)	5 (1%)
	MILD	21 (4%)	30 (6%)	33 (6%)	17 (3%)	11 (2%)	4 (1%)	4 (1%)	5 (1%)
	MODERATE	2 (<1%)	4 (1%)	7 (1%)	6 (1%)	3 (1%)	1 (<1%)	0	0
	SEVERE	0	1 (<1%)	3 (1%)	0	1 (<1%)	0	0	0
Rash	N	539	531	531	530	531	531	531	531
	ANY	0	1 (<1%)	6 (1%)	7 (1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
	OTHER	0	0	2 (<1%)	3 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
	URTICARIAL	0	1 (<1%)	4 (1%)	4 (1%)	0	0	1 (<1%)	0
Fever (>= 38C)	N	536	521	524	522	522	521	522	518
	YES	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
	NO	536 (100%)	521 (100%)	522 (100%)	521 (100%)	521 (100%)	521 (100%)	522 (100%)	518 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
OTHER									
Stayed Home	N	0	530	532	530	532	531	530	531
	YES	0	2 (<1%)	5 (1%)	4 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	NO	0	528 (100%)	527 (99%)	526 (99%)	531 (100%)	530 (100%)	529 (100%)	531 (100%)
Analgesic Antipyretics	N	538	532	532	530	532	530	531	531
	YES	1 (<1%)	27 (5%)	33 (6%)	20 (4%)	11 (2%)	6 (1%)	4 (1%)	2 (<1%)
	NO	537 (100%)	505 (95%)	499 (94%)	510 (96%)	521 (98%)	524 (99%)	527 (99%)	529 (100%)
Temperature (C)	N	536	521	524	522	522	521	522	518
	<38 C	536 (100%)	521 (100%)	522 (100%)	521 (100%)	521 (100%)	521 (100%)	522 (100%)	518 (100%)
	38 - 38.9 C	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
INJECTION SITE									
Pain	N	541	508	509	509	509	509	509	509
	ANY	115 (21%)	60 (12%)	44 (9%)	15 (3%)	8 (2%)	3 (1%)	0	0
	MILD	94 (17%)	41 (8%)	34 (7%)	12 (2%)	8 (2%)	3 (1%)	0	0
	MODERATE	20 (4%)	18 (4%)	9 (2%)	3 (1%)	0	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	541	508	509	509	509	509	509	509
	ANY	46 (9%)	4 (1%)	1 (<1%)	10 (2%)	4 (1%)	0	1 (<1%)	0
	>0 - 25 mm	46 (9%)	4 (1%)	1 (<1%)	6 (1%)	3 (1%)	0	1 (<1%)	0
	>25 - 50 mm	0	0	0	3 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	0	0	1 (<1%)	0	0	0	0
Induration (mm)	N	541	508	509	509	509	509	509	509
	ANY	19 (4%)	12 (2%)	14 (3%)	19 (4%)	6 (1%)	0	0	0
	>0 - 25 mm	19 (4%)	9 (2%)	12 (2%)	12 (2%)	5 (1%)	0	0	0
	>25 - 50 mm	0	1 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	2 (<1%)	1 (<1%)	3 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	541	509	509	509	509	509	509	509
	ANY	10 (2%)	12 (2%)	22 (4%)	8 (2%)	4 (1%)	3 (1%)	4 (1%)	3 (1%)
	MILD	7 (1%)	7 (1%)	17 (3%)	6 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)
	MODERATE	2 (<1%)	5 (1%)	3 (1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0	0
Nausea	N	541	509	509	509	509	509	509	509
	ANY	7 (1%)	16 (3%)	28 (6%)	6 (1%)	6 (1%)	2 (<1%)	5 (1%)	2 (<1%)
	MILD	6 (1%)	10 (2%)	20 (4%)	4 (1%)	3 (1%)	2 (<1%)	4 (1%)	1 (<1%)
	MODERATE	1 (<1%)	5 (1%)	7 (1%)	2 (<1%)	3 (1%)	0	1 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	1 (<1%)	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
SYSTEMIC									
Malaise	N	541	509	509	509	509	509	509	509
	ANY	8 (1%)	34 (7%)	38 (7%)	19 (4%)	3 (1%)	3 (1%)	1 (<1%)	4 (1%)
	MILD	5 (1%)	29 (6%)	30 (6%)	15 (3%)	1 (<1%)	3 (1%)	1 (<1%)	2 (<1%)
	MODERATE	3 (1%)	3 (1%)	7 (1%)	3 (1%)	2 (<1%)	0	0	2 (<1%)
	SEVERE	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
Myalgia	N	541	509	509	509	509	509	509	509
	ANY	24 (4%)	23 (5%)	37 (7%)	11 (2%)	3 (1%)	1 (<1%)	3 (1%)	2 (<1%)
	MILD	17 (3%)	16 (3%)	27 (5%)	7 (1%)	2 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
	MODERATE	7 (1%)	6 (1%)	7 (1%)	3 (1%)	1 (<1%)	0	0	1 (<1%)
	SEVERE	0	1 (<1%)	3 (1%)	1 (<1%)	0	0	0	0
Arthralgia	N	541	509	509	509	509	509	509	509
	ANY	12 (2%)	8 (2%)	23 (5%)	8 (2%)	4 (1%)	3 (1%)	1 (<1%)	3 (1%)
	MILD	10 (2%)	6 (1%)	16 (3%)	7 (1%)	4 (1%)	3 (1%)	0	1 (<1%)
	MODERATE	2 (<1%)	2 (<1%)	6 (1%)	0	0	0	1 (<1%)	1 (<1%)
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Headache	N	541	508	509	509	509	509	509	509
	ANY	42 (8%)	67 (13%)	46 (9%)	17 (3%)	11 (2%)	3 (1%)	5 (1%)	3 (1%)
	MILD	29 (5%)	50 (10%)	32 (6%)	9 (2%)	9 (2%)	1 (<1%)	2 (<1%)	2 (<1%)
	MODERATE	10 (2%)	12 (2%)	11 (2%)	6 (1%)	2 (<1%)	2 (<1%)	3 (1%)	1 (<1%)
	SEVERE	3 (1%)	5 (1%)	3 (1%)	2 (<1%)	0	0	0	0
Rash	N	540	509	509	509	507	508	509	509
	ANY	0	4 (1%)	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	1 (<1%)	0
	OTHER	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	URTICARIAL	0	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)	0
Fever (>= 38C)	N	541	498	504	504	505	504	502	494
	YES	3 (1%)	2 (<1%)	8 (2%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	NO	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
OTHER									
Stayed Home	N	0	509	509	509	509	508	509	509
	YES	0	21 (4%)	13 (3%)	4 (1%)	2 (<1%)	0	0	0
	NO	0	488 (96%)	496 (97%)	505 (99%)	507 (100%)	508 (100%)	509 (100%)	509 (100%)
Analgesic Antipyretics	N	541	508	508	508	508	508	508	508
	YES	0	14 (3%)	31 (6%)	11 (2%)	7 (1%)	2 (<1%)	4 (1%)	4 (1%)
	NO	541 (100%)	494 (97%)	477 (94%)	497 (98%)	501 (99%)	506 (100%)	504 (99%)	504 (99%)
Temperature (C)	N	541	498	504	504	505	504	502	494
	<38 C	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)
	38 - 38.9 C	3 (1%)	2 (<1%)	7 (1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
INJECTION SITE									
Pain	N	539	500	502	502	502	502	502	501
	ANY	109 (20%)	188 (38%)	68 (14%)	11 (2%)	3 (1%)	4 (1%)	0	0
	MILD	88 (16%)	137 (27%)	50 (10%)	9 (2%)	1 (<1%)	3 (1%)	0	0
	MODERATE	19 (4%)	48 (10%)	15 (3%)	2 (<1%)	2 (<1%)	1 (<1%)	0	0
	SEVERE	2 (<1%)	3 (1%)	3 (1%)	0	0	0	0	0
Erythema (mm)	N	539	500	502	502	502	502	502	502
	ANY	35 (6%)	8 (2%)	11 (2%)	12 (2%)	4 (1%)	0	0	0
	>0 - 25 mm	34 (6%)	8 (2%)	10 (2%)	11 (2%)	4 (1%)	0	0	0
	>25 - 50 mm	1 (<1%)	0	1 (<1%)	0	0	0	0	0
	> 50 mm	0	0	0	1 (<1%)	0	0	0	0
Induration (mm)	N	539	500	502	502	502	502	501	501
	ANY	15 (3%)	33 (7%)	44 (9%)	13 (3%)	1 (<1%)	2 (<1%)	0	1 (<1%)
	>0 - 25 mm	13 (2%)	27 (5%)	30 (6%)	12 (2%)	1 (<1%)	2 (<1%)	0	1 (<1%)
	>25 - 50 mm	1 (<1%)	5 (1%)	8 (2%)	1 (<1%)	0	0	0	0
	> 50 mm	1 (<1%)	1 (<1%)	6 (1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	539	501	502	502	502	502	502	502
	ANY	14 (3%)	12 (2%)	20 (4%)	8 (2%)	5 (1%)	6 (1%)	4 (1%)	1 (<1%)
	MILD	9 (2%)	8 (2%)	16 (3%)	7 (1%)	4 (1%)	5 (1%)	4 (1%)	1 (<1%)
	MODERATE	5 (1%)	4 (1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
	SEVERE	0	0	2 (<1%)	0	0	0	0	0
Nausea	N	539	501	502	502	502	502	502	502
	ANY	12 (2%)	18 (4%)	24 (5%)	12 (2%)	5 (1%)	6 (1%)	2 (<1%)	3 (1%)
	MILD	11 (2%)	12 (2%)	17 (3%)	11 (2%)	4 (1%)	5 (1%)	2 (<1%)	2 (<1%)
	MODERATE	1 (<1%)	6 (1%)	6 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
	SEVERE	0	0	1 (<1%)	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
SYSTEMIC									
Malaise	N	539	501	502	502	502	502	502	502
	ANY	11 (2%)	36 (7%)	41 (8%)	11 (2%)	6 (1%)	4 (1%)	3 (1%)	3 (1%)
	MILD	8 (1%)	26 (5%)	33 (7%)	6 (1%)	5 (1%)	2 (<1%)	3 (1%)	1 (<1%)
	MODERATE	2 (<1%)	9 (2%)	5 (1%)	5 (1%)	1 (<1%)	2 (<1%)	0	2 (<1%)
	SEVERE	1 (<1%)	1 (<1%)	3 (1%)	0	0	0	0	0
Myalgia	N	539	501	502	502	502	502	502	502
	ANY	29 (5%)	59 (12%)	28 (6%)	15 (3%)	4 (1%)	2 (<1%)	1 (<1%)	3 (1%)
	MILD	20 (4%)	40 (8%)	23 (5%)	11 (2%)	3 (1%)	2 (<1%)	1 (<1%)	3 (1%)
	MODERATE	8 (1%)	17 (3%)	4 (1%)	2 (<1%)	1 (<1%)	0	0	0
	SEVERE	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	0	0	0	0
Arthralgia	N	539	501	502	502	502	502	502	502
	ANY	18 (3%)	27 (5%)	17 (3%)	6 (1%)	2 (<1%)	3 (1%)	3 (1%)	0
	MILD	12 (2%)	21 (4%)	13 (3%)	4 (1%)	1 (<1%)	3 (1%)	2 (<1%)	0
	MODERATE	4 (1%)	6 (1%)	3 (1%)	2 (<1%)	1 (<1%)	0	1 (<1%)	0
	SEVERE	2 (<1%)	0	1 (<1%)	0	0	0	0	0
Headache	N	539	501	502	502	502	502	502	502
	ANY	53 (10%)	59 (12%)	45 (9%)	16 (3%)	13 (3%)	7 (1%)	4 (1%)	3 (1%)
	MILD	37 (7%)	35 (7%)	37 (7%)	13 (3%)	10 (2%)	5 (1%)	2 (<1%)	3 (1%)
	MODERATE	13 (2%)	19 (4%)	8 (2%)	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	0
	SEVERE	3 (1%)	5 (1%)	0	1 (<1%)	2 (<1%)	0	0	0
Rash	N	538	501	502	502	502	502	501	502
	ANY	2 (<1%)	1 (<1%)	8 (2%)	4 (1%)	2 (<1%)	0	3 (1%)	0
	OTHER	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0
	URTICARIAL	1 (<1%)	1 (<1%)	7 (1%)	4 (1%)	2 (<1%)	0	2 (<1%)	0
Fever (>= 38C)	N	539	493	499	499	498	492	491	485
	YES	1 (<1%)	4 (1%)	5 (1%)	2 (<1%)	0	1 (<1%)	3 (1%)	1 (<1%)
	NO	538 (100%)	489 (99%)	494 (99%)	497 (100%)	498 (100%)	491 (100%)	488 (99%)	484 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=539)	6HR (N=539)	DAY 2 (N=539)	DAY 3 (N=539)	DAY 4 (N=539)	DAY 5 (N=539)	DAY 6 (N=539)	DAY 7 (N=539)
OTHER									
Stayed Home	N	0	501	502	502	502	502	502	501
	YES	0	21 (4%)	10 (2%)	6 (1%)	1 (<1%)	0	0	1 (<1%)
	NO	0	480 (96%)	492 (98%)	496 (99%)	501 (100%)	502 (100%)	502 (100%)	500 (100%)
Analgesic Antipyretics	N	539	503	503	503	503	503	503	503
	YES	3 (1%)	33 (7%)	30 (6%)	9 (2%)	7 (1%)	3 (1%)	3 (1%)	4 (1%)
	NO	536 (99%)	470 (93%)	473 (94%)	494 (98%)	496 (99%)	500 (99%)	500 (99%)	499 (99%)
Temperature (C)	N	539	493	499	499	498	492	491	485
	<38 C	538 (100%)	489 (99%)	494 (99%)	497 (100%)	498 (100%)	491 (100%)	488 (99%)	484 (100%)
	38 - 38.9 C	0	3 (1%)	3 (1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
	39.0 - 39.9 C	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0	1 (<1%)	0
	>= 40 C	0	0	0	0	0	0	0	0

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects 30M (N=307)	6HR (N=307)	DAY 2 (N=307)	DAY 3 (N=307)	DAY 4 (N=307)	DAY 5 (N=307)	DAY 6 (N=307)	DAY 7 (N=307)
INJECTION SITE									
Pain	N	307	297	297	297	297	297	297	297
	ANY	37 (12%)	54 (18%)	45 (15%)	9 (3%)	6 (2%)	0	0	0
	MILD	33 (11%)	49 (16%)	37 (12%)	9 (3%)	6 (2%)	0	0	0
	MODERATE	4 (1%)	5 (2%)	8 (3%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	307	297	297	297	297	297	297	297
	ANY	26 (8%)	8 (3%)	21 (7%)	5 (2%)	1 (<1%)	3 (1%)	2 (1%)	0
	>0 - 25 mm	25 (8%)	7 (2%)	16 (5%)	4 (1%)	0	2 (1%)	1 (<1%)	0
	>25 - 50 mm	1 (<1%)	0	5 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
	> 50 mm	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Induration (mm)	N	307	297	297	297	297	297	297	297
	ANY	11 (4%)	6 (2%)	18 (6%)	7 (2%)	1 (<1%)	2 (1%)	1 (<1%)	0
	>0 - 25 mm	11 (4%)	6 (2%)	14 (5%)	3 (1%)	1 (<1%)	1 (<1%)	0	0
	>25 - 50 mm	0	0	4 (1%)	3 (1%)	0	1 (<1%)	1 (<1%)	0
	> 50 mm	0	0	0	1 (<1%)	0	0	0	0
SYSTEMIC									
Chills	N	307	297	297	297	297	297	297	297
	ANY	2 (1%)	3 (1%)	7 (2%)	0	1 (<1%)	0	0	1 (<1%)
	MILD	2 (1%)	3 (1%)	6 (2%)	0	1 (<1%)	0	0	1 (<1%)
	MODERATE	0	0	0	0	0	0	0	0
	SEVERE	0	0	1 (<1%)	0	0	0	0	0
Nausea	N	307	297	297	297	297	297	297	297
	ANY	2 (1%)	9 (3%)	8 (3%)	3 (1%)	1 (<1%)	4 (1%)	1 (<1%)	0
	MILD	1 (<1%)	9 (3%)	4 (1%)	3 (1%)	0	2 (1%)	1 (<1%)	0
	MODERATE	1 (<1%)	0	4 (1%)	0	1 (<1%)	0	0	0
	SEVERE	0	0	0	0	0	2 (1%)	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=307)	6HR (N=307)	DAY 2 (N=307)	DAY 3 (N=307)	DAY 4 (N=307)	DAY 5 (N=307)	DAY 6 (N=307)	DAY 7 (N=307)
SYSTEMIC									
Malaise	N	307	297	297	297	297	297	297	297
	ANY	3 (1%)	6 (2%)	18 (6%)	6 (2%)	2 (1%)	2 (1%)	2 (1%)	1 (<1%)
	MILD	2 (1%)	6 (2%)	10 (3%)	6 (2%)	2 (1%)	1 (<1%)	1 (<1%)	0
	MODERATE	0	0	7 (2%)	0	0	0	1 (<1%)	1 (<1%)
	SEVERE	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0
Myalgia	N	307	297	297	297	297	297	297	297
	ANY	2 (1%)	17 (6%)	23 (8%)	10 (3%)	2 (1%)	0	1 (<1%)	0
	MILD	1 (<1%)	15 (5%)	15 (5%)	10 (3%)	2 (1%)	0	0	0
	MODERATE	1 (<1%)	2 (1%)	8 (3%)	0	0	0	1 (<1%)	0
	SEVERE	0	0	0	0	0	0	0	0
Arthralgia	N	307	297	297	297	297	297	297	297
	ANY	0	4 (1%)	8 (3%)	4 (1%)	1 (<1%)	1 (<1%)	0	0
	MILD	0	3 (1%)	6 (2%)	3 (1%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	0	1 (<1%)	2 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	307	297	297	297	297	297	297	297
	ANY	2 (1%)	28 (9%)	28 (9%)	11 (4%)	10 (3%)	4 (1%)	2 (1%)	2 (1%)
	MILD	2 (1%)	23 (8%)	18 (6%)	9 (3%)	6 (2%)	4 (1%)	0	2 (1%)
	MODERATE	0	5 (2%)	10 (3%)	2 (1%)	4 (1%)	0	1 (<1%)	0
	SEVERE	0	0	0	0	0	0	1 (<1%)	0
Rash	N	307	297	297	297	297	297	297	297
	ANY	2 (1%)	3 (1%)	2 (1%)	0	2 (1%)	0	0	0
	OTHER	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0
	URTICARIAL	1 (<1%)	2 (1%)	1 (<1%)	0	1 (<1%)	0	0	0
Fever (>= 38C)	N	306	293	294	294	293	293	294	292
	YES	0	0	2 (1%)	0	1 (<1%)	0	0	1 (<1%)
	NO	306 (100%)	293 (100%)	292 (99%)	294 (100%)	292 (100%)	293 (100%)	294 (100%)	291 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects 30M (N=307)	6HR (N=307)	DAY 2 (N=307)	DAY 3 (N=307)	DAY 4 (N=307)	DAY 5 (N=307)	DAY 6 (N=307)	DAY 7 (N=307)
OTHER									
Stayed Home	N	0	297	297	297	297	297	297	297
	YES	0	1 (<1%)	5 (2%)	1 (<1%)	0	0	0	0
	NO	0	296 (100%)	292 (98%)	296 (100%)	297 (100%)	297 (100%)	297 (100%)	297 (100%)
Analgesic Antipyretics	N	306	297	297	296	297	297	297	297
	YES	4 (1%)	10 (3%)	25 (8%)	11 (4%)	8 (3%)	2 (1%)	1 (<1%)	3 (1%)
	NO	302 (99%)	287 (97%)	272 (92%)	285 (96%)	289 (97%)	295 (99%)	296 (100%)	294 (99%)
Temperature (C)	N	306	293	294	294	293	293	294	292
	<38 C	306 (100%)	293 (100%)	292 (99%)	294 (100%)	292 (100%)	293 (100%)	294 (100%)	291 (100%)
	38 - 38.9 C	0	0	1 (<1%)	0	0	0	0	1 (<1%)
	39.0 - 39.9 C	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=105)	6HR (N=105)	DAY 2 (N=105)	DAY 3 (N=105)	DAY 4 (N=105)	DAY 5 (N=105)	DAY 6 (N=105)	DAY 7 (N=105)
INJECTION SITE									
Pain	N	105	103	103	103	103	103	103	103
	ANY	12 (11%)	28 (27%)	5 (5%)	0	0	0	0	0
	MILD	10 (10%)	25 (24%)	4 (4%)	0	0	0	0	0
	MODERATE	2 (2%)	3 (3%)	1 (1%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	105	103	103	103	103	103	103	103
	ANY	3 (3%)	2 (2%)	1 (1%)	0	0	0	1 (1%)	0
	>0 - 25 mm	3 (3%)	2 (2%)	1 (1%)	0	0	0	0	0
	>25 - 50 mm	0	0	0	0	0	0	1 (1%)	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	105	103	103	103	103	103	103	103
	ANY	2 (2%)	1 (1%)	3 (3%)	0	0	0	0	0
	>0 - 25 mm	2 (2%)	1 (1%)	3 (3%)	0	0	0	0	0
	>25 - 50 mm	0	0	0	0	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
SYSTEMIC									
Chills	N	105	103	103	103	103	103	103	103
	ANY	1 (1%)	0	2 (2%)	1 (1%)	0	1 (1%)	2 (2%)	0
	MILD	1 (1%)	0	1 (1%)	0	0	0	2 (2%)	0
	MODERATE	0	0	1 (1%)	1 (1%)	0	1 (1%)	0	0
	SEVERE	0	0	0	0	0	0	0	0
Nausea	N	105	103	103	103	103	103	103	103
	ANY	1 (1%)	1 (1%)	2 (2%)	0	1 (1%)	2 (2%)	1 (1%)	1 (1%)
	MILD	1 (1%)	1 (1%)	1 (1%)	0	0	1 (1%)	1 (1%)	1 (1%)
	MODERATE	0	0	1 (1%)	0	1 (1%)	1 (1%)	0	0
	SEVERE	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=105)	6HR (N=105)	DAY 2 (N=105)	DAY 3 (N=105)	DAY 4 (N=105)	DAY 5 (N=105)	DAY 6 (N=105)	DAY 7 (N=105)
SYSTEMIC									
Malaise	N	105	103	103	103	103	103	103	103
	ANY	0	5 (5%)	3 (3%)	1 (1%)	1 (1%)	3 (3%)	1 (1%)	1 (1%)
	MILD	0	3 (3%)	2 (2%)	0	0	2 (2%)	1 (1%)	0
	MODERATE	0	1 (1%)	1 (1%)	1 (1%)	0	1 (1%)	0	1 (1%)
	SEVERE	0	1 (1%)	0	0	1 (1%)	0	0	0
Myalgia	N	105	103	103	103	103	103	103	103
	ANY	1 (1%)	10 (10%)	4 (4%)	1 (1%)	1 (1%)	1 (1%)	3 (3%)	0
	MILD	1 (1%)	9 (9%)	2 (2%)	1 (1%)	0	0	2 (2%)	0
	MODERATE	0	0	2 (2%)	0	1 (1%)	1 (1%)	1 (1%)	0
	SEVERE	0	1 (1%)	0	0	0	0	0	0
Arthralgia	N	105	103	103	103	103	103	103	103
	ANY	1 (1%)	2 (2%)	1 (1%)	0	0	2 (2%)	0	0
	MILD	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0
	MODERATE	0	1 (1%)	1 (1%)	0	0	1 (1%)	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	105	103	103	103	103	103	103	103
	ANY	1 (1%)	8 (8%)	5 (5%)	4 (4%)	3 (3%)	0	2 (2%)	0
	MILD	0	4 (4%)	3 (3%)	4 (4%)	2 (2%)	0	2 (2%)	0
	MODERATE	1 (1%)	2 (2%)	2 (2%)	0	1 (1%)	0	0	0
	SEVERE	0	2 (2%)	0	0	0	0	0	0
Rash	N	105	103	103	103	103	103	103	103
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	105	100	102	102	101	101	101	101
	YES	0	0	0	1 (1%)	0	1 (1%)	0	0
	NO	105 (100%)	100 (100%)	102 (100%)	101 (99%)	101 (100%)	100 (99%)	101 (100%)	101 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=105)	6HR (N=105)	DAY 2 (N=105)	DAY 3 (N=105)	DAY 4 (N=105)	DAY 5 (N=105)	DAY 6 (N=105)	DAY 7 (N=105)
OTHER									
Stayed Home	N	0	103	103	103	103	103	103	103
	YES	0	1 (1%)	0	0	1 (1%)	1 (1%)	0	0
	NO	0	102 (99%)	103 (100%)	103 (100%)	102 (99%)	102 (99%)	103 (100%)	103 (100%)
Analgesic Antipyretics	N	105	103	103	103	103	103	103	103
	YES	2 (2%)	3 (3%)	3 (3%)	6 (6%)	2 (2%)	1 (1%)	1 (1%)	1 (1%)
	NO	103 (98%)	100 (97%)	100 (97%)	97 (94%)	101 (98%)	102 (99%)	102 (99%)	102 (99%)
Temperature (C)	N	105	100	102	102	101	101	101	101
	<38 C	105 (100%)	100 (100%)	102 (100%)	101 (99%)	101 (100%)	100 (99%)	101 (100%)	101 (100%)
	38 - 38.9 C	0	0	0	0	0	1 (1%)	0	0
	39.0 - 39.9 C	0	0	0	1 (1%)	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=838)	6HR (N=838)	DAY 2 (N=838)	DAY 3 (N=838)	DAY 4 (N=838)	DAY 5 (N=838)	DAY 6 (N=838)	DAY 7 (N=838)
INJECTION SITE									
Pain	N	837	835	837	837	836	835	835	833
	ANY	167 (20%)	113 (14%)	58 (7%)	14 (2%)	1 (<1%)	4 (<1%)	0	2 (<1%)
	MILD	144 (17%)	91 (11%)	49 (6%)	11 (1%)	1 (<1%)	3 (<1%)	0	2 (<1%)
	MODERATE	22 (3%)	19 (2%)	8 (1%)	3 (<1%)	0	1 (<1%)	0	0
	SEVERE	1 (<1%)	3 (<1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	837	835	836	835	836	835	835	833
	ANY	71 (8%)	14 (2%)	26 (3%)	6 (1%)	1 (<1%)	2 (<1%)	1 (<1%)	5 (1%)
	>0 - 25 mm	69 (8%)	13 (2%)	21 (3%)	5 (1%)	1 (<1%)	0	1 (<1%)	4 (<1%)
	>25 - 50 mm	2 (<1%)	0	3 (<1%)	0	0	2 (<1%)	0	0
	> 50 mm	0	1 (<1%)	2 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Induration (mm)	N	837	834	835	835	835	834	834	832
	ANY	39 (5%)	21 (3%)	30 (4%)	8 (1%)	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
	>0 - 25 mm	38 (5%)	19 (2%)	25 (3%)	7 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
	>25 - 50 mm	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)	0	0
	> 50 mm	0	1 (<1%)	2 (<1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	837	836	838	838	838	838	838	836
	ANY	7 (1%)	14 (2%)	23 (3%)	8 (1%)	6 (1%)	3 (<1%)	4 (<1%)	0
	MILD	5 (1%)	12 (1%)	10 (1%)	6 (1%)	6 (1%)	1 (<1%)	3 (<1%)	0
	MODERATE	1 (<1%)	2 (<1%)	10 (1%)	0	0	1 (<1%)	1 (<1%)	0
	SEVERE	1 (<1%)	0	3 (<1%)	2 (<1%)	0	1 (<1%)	0	0
Nausea	N	837	836	838	838	838	838	838	836
	ANY	6 (1%)	24 (3%)	15 (2%)	5 (1%)	9 (1%)	7 (1%)	3 (<1%)	0
	MILD	5 (1%)	20 (2%)	12 (1%)	5 (1%)	7 (1%)	5 (1%)	3 (<1%)	0
	MODERATE	0	4 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	0
	SEVERE	1 (<1%)	0	1 (<1%)	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=838)	6HR (N=838)	DAY 2 (N=838)	DAY 3 (N=838)	DAY 4 (N=838)	DAY 5 (N=838)	DAY 6 (N=838)	DAY 7 (N=838)
SYSTEMIC									
Malaise	N	837	836	838	838	838	838	838	836
	ANY	13 (2%)	50 (6%)	66 (8%)	13 (2%)	8 (1%)	6 (1%)	7 (1%)	2 (<1%)
	MILD	11 (1%)	45 (5%)	42 (5%)	7 (1%)	5 (1%)	4 (<1%)	6 (1%)	2 (<1%)
	MODERATE	2 (<1%)	2 (<1%)	19 (2%)	3 (<1%)	1 (<1%)	2 (<1%)	0	0
	SEVERE	0	3 (<1%)	5 (1%)	3 (<1%)	2 (<1%)	0	1 (<1%)	0
Myalgia	N	837	836	838	838	838	838	838	836
	ANY	8 (1%)	28 (3%)	46 (5%)	12 (1%)	2 (<1%)	5 (1%)	2 (<1%)	2 (<1%)
	MILD	7 (1%)	23 (3%)	30 (4%)	8 (1%)	2 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
	MODERATE	1 (<1%)	3 (<1%)	12 (1%)	1 (<1%)	0	3 (<1%)	0	0
	SEVERE	0	2 (<1%)	4 (<1%)	3 (<1%)	0	0	1 (<1%)	0
Arthralgia	N	837	835	837	838	838	838	838	836
	ANY	2 (<1%)	15 (2%)	20 (2%)	11 (1%)	1 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)
	MILD	2 (<1%)	11 (1%)	14 (2%)	8 (1%)	0	1 (<1%)	3 (<1%)	1 (<1%)
	MODERATE	0	3 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	1 (<1%)	3 (<1%)	1 (<1%)	0	0	0	0
Headache	N	837	836	838	838	838	838	838	836
	ANY	28 (3%)	76 (9%)	63 (8%)	26 (3%)	20 (2%)	5 (1%)	8 (1%)	3 (<1%)
	MILD	22 (3%)	59 (7%)	46 (5%)	16 (2%)	13 (2%)	2 (<1%)	8 (1%)	3 (<1%)
	MODERATE	6 (1%)	13 (2%)	13 (2%)	8 (1%)	5 (1%)	3 (<1%)	0	0
	SEVERE	0	4 (<1%)	4 (<1%)	2 (<1%)	2 (<1%)	0	0	0
Rash	N	837	836	838	838	837	837	837	835
	ANY	2 (<1%)	6 (1%)	7 (1%)	5 (1%)	4 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
	OTHER	1 (<1%)	2 (<1%)	4 (<1%)	2 (<1%)	0	0	0	0
	URTICARIAL	1 (<1%)	4 (<1%)	3 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
Fever (>= 38C)	N	837	768	770	766	764	761	761	752
	YES	1 (<1%)	6 (1%)	7 (1%)	7 (1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
	NO	836 (100%)	762 (99%)	763 (99%)	759 (99%)	763 (100%)	760 (100%)	758 (100%)	751 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=838)	6HR (N=838)	DAY 2 (N=838)	DAY 3 (N=838)	DAY 4 (N=838)	DAY 5 (N=838)	DAY 6 (N=838)	DAY 7 (N=838)
OTHER									
Stayed Home	N	0	834	835	836	835	835	835	832
	YES	0	13 (2%)	15 (2%)	6 (1%)	4 (<1%)	0	1 (<1%)	1 (<1%)
	NO	0	821 (98%)	820 (98%)	830 (99%)	831 (100%)	835 (100%)	834 (100%)	831 (100%)
Analgesic Antipyretics	N	837	834	835	836	835	833	833	830
	YES	4 (<1%)	41 (5%)	47 (6%)	18 (2%)	12 (1%)	11 (1%)	8 (1%)	3 (<1%)
	NO	833 (100%)	793 (95%)	788 (94%)	818 (98%)	823 (99%)	822 (99%)	825 (99%)	827 (100%)
Temperature (C)	N	837	768	770	766	764	761	761	752
	<38 C	836 (100%)	762 (99%)	763 (99%)	759 (99%)	763 (100%)	760 (100%)	758 (100%)	751 (100%)
	38 - 38.9 C	1 (<1%)	4 (1%)	5 (1%)	4 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
	39.0 - 39.9 C	0	2 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0
	>= 40 C	0	0	1 (<1%)	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=464)	6HR (N=464)	DAY 2 (N=464)	DAY 3 (N=464)	DAY 4 (N=464)	DAY 5 (N=464)	DAY 6 (N=464)	DAY 7 (N=464)
INJECTION SITE									
Pain	N	464	453	464	464	462	463	462	462
	ANY	99 (21%)	70 (15%)	48 (10%)	12 (3%)	1 (<1%)	0	1 (<1%)	0
	MILD	76 (16%)	60 (13%)	40 (9%)	10 (2%)	1 (<1%)	0	1 (<1%)	0
	MODERATE	22 (5%)	10 (2%)	5 (1%)	1 (<1%)	0	0	0	0
	SEVERE	1 (<1%)	0	3 (1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	464	450	461	461	460	461	460	460
	ANY	27 (6%)	11 (2%)	13 (3%)	5 (1%)	0	1 (<1%)	0	0
	>0 - 25 mm	26 (6%)	8 (2%)	9 (2%)	2 (<1%)	0	1 (<1%)	0	0
	>25 - 50 mm	1 (<1%)	2 (<1%)	2 (<1%)	0	0	0	0	0
	> 50 mm	0	1 (<1%)	2 (<1%)	3 (1%)	0	0	0	0
Induration (mm)	N	464	451	462	462	461	462	461	461
	ANY	23 (5%)	12 (3%)	21 (5%)	3 (1%)	1 (<1%)	1 (<1%)	0	0
	>0 - 25 mm	22 (5%)	10 (2%)	15 (3%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0
	>25 - 50 mm	1 (<1%)	2 (<1%)	3 (1%)	1 (<1%)	0	0	0	0
	> 50 mm	0	0	3 (1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	464	453	464	464	463	464	463	463
	ANY	2 (<1%)	10 (2%)	12 (3%)	5 (1%)	5 (1%)	3 (1%)	1 (<1%)	1 (<1%)
	MILD	2 (<1%)	6 (1%)	9 (2%)	4 (1%)	4 (1%)	3 (1%)	1 (<1%)	1 (<1%)
	MODERATE	0	4 (1%)	2 (<1%)	0	1 (<1%)	0	0	0
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Nausea	N	464	453	464	464	463	464	463	463
	ANY	4 (1%)	12 (3%)	12 (3%)	4 (1%)	2 (<1%)	3 (1%)	2 (<1%)	4 (1%)
	MILD	3 (1%)	10 (2%)	10 (2%)	3 (1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
	MODERATE	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	0	0	0	2 (<1%)
	SEVERE	0	0	0	0	0	1 (<1%)	0	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=464)	6HR (N=464)	DAY 2 (N=464)	DAY 3 (N=464)	DAY 4 (N=464)	DAY 5 (N=464)	DAY 6 (N=464)	DAY 7 (N=464)
SYSTEMIC									
Malaise	N	464	453	464	464	463	464	463	463
	ANY	16 (3%)	32 (7%)	19 (4%)	18 (4%)	5 (1%)	4 (1%)	6 (1%)	4 (1%)
	MILD	15 (3%)	25 (6%)	12 (3%)	12 (3%)	4 (1%)	3 (1%)	5 (1%)	4 (1%)
	MODERATE	1 (<1%)	7 (2%)	6 (1%)	5 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Myalgia	N	464	453	464	464	463	464	463	463
	ANY	5 (1%)	16 (4%)	21 (5%)	9 (2%)	6 (1%)	1 (<1%)	2 (<1%)	3 (1%)
	MILD	5 (1%)	11 (2%)	14 (3%)	2 (<1%)	4 (1%)	1 (<1%)	1 (<1%)	2 (<1%)
	MODERATE	0	5 (1%)	6 (1%)	7 (2%)	2 (<1%)	0	1 (<1%)	1 (<1%)
	SEVERE	0	0	1 (<1%)	0	0	0	0	0
Arthralgia	N	464	453	464	464	463	464	463	463
	ANY	3 (1%)	4 (1%)	16 (3%)	4 (1%)	5 (1%)	1 (<1%)	0	3 (1%)
	MILD	3 (1%)	3 (1%)	12 (3%)	1 (<1%)	4 (1%)	1 (<1%)	0	3 (1%)
	MODERATE	0	1 (<1%)	4 (1%)	3 (1%)	1 (<1%)	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	464	453	464	464	463	464	463	463
	ANY	18 (4%)	45 (10%)	28 (6%)	20 (4%)	7 (2%)	7 (2%)	5 (1%)	5 (1%)
	MILD	13 (3%)	29 (6%)	22 (5%)	13 (3%)	6 (1%)	5 (1%)	3 (1%)	3 (1%)
	MODERATE	4 (1%)	12 (3%)	5 (1%)	4 (1%)	1 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	4 (1%)	1 (<1%)	3 (1%)	0	0	0	0
Rash	N	464	453	464	464	463	464	463	463
	ANY	0	4 (1%)	4 (1%)	3 (1%)	1 (<1%)	0	1 (<1%)	0
	OTHER	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
	URTICARIAL	0	3 (1%)	3 (1%)	2 (<1%)	1 (<1%)	0	0	0
Fever (>= 38C)	N	464	415	420	417	409	410	408	406
	YES	0	4 (1%)	3 (1%)	4 (1%)	1 (<1%)	3 (1%)	0	1 (<1%)
	NO	464 (100%)	411 (99%)	417 (99%)	413 (99%)	408 (100%)	407 (99%)	408 (100%)	405 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=464)	6HR (N=464)	DAY 2 (N=464)	DAY 3 (N=464)	DAY 4 (N=464)	DAY 5 (N=464)	DAY 6 (N=464)	DAY 7 (N=464)
OTHER									
Stayed Home	N	0	452	463	463	462	463	462	462
	YES	0	6 (1%)	3 (1%)	5 (1%)	3 (1%)	3 (1%)	0	2 (<1%)
	NO	0	446 (99%)	460 (99%)	458 (99%)	459 (99%)	460 (99%)	462 (100%)	460 (100%)
Analgesic Antipyretics	N	464	452	463	463	462	463	461	462
	YES	0	26 (6%)	17 (4%)	6 (1%)	6 (1%)	4 (1%)	2 (<1%)	5 (1%)
	NO	464 (100%)	426 (94%)	446 (96%)	457 (99%)	456 (99%)	459 (99%)	459 (100%)	457 (99%)
Temperature (C)	N	464	415	420	417	409	410	408	406
	<38 C	464 (100%)	411 (99%)	417 (99%)	413 (99%)	408 (100%)	407 (99%)	408 (100%)	405 (100%)
	38 - 38.9 C	0	4 (1%)	3 (1%)	3 (1%)	1 (<1%)	2 (<1%)	0	0
	39.0 - 39.9 C	0	0	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=711)	6HR (N=711)	DAY 2 (N=711)	DAY 3 (N=711)	DAY 4 (N=711)	DAY 5 (N=711)	DAY 6 (N=711)	DAY 7 (N=711)
INJECTION SITE									
Pain	N	711	709	707	709	709	709	709	709
	ANY	66 (9%)	74 (10%)	70 (10%)	21 (3%)	6 (1%)	1 (<1%)	1 (<1%)	1 (<1%)
	MILD	61 (9%)	69 (10%)	64 (9%)	16 (2%)	5 (1%)	1 (<1%)	0	0
	MODERATE	5 (1%)	5 (1%)	6 (1%)	5 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	711	709	708	709	709	709	709	709
	ANY	29 (4%)	28 (4%)	29 (4%)	9 (1%)	4 (1%)	0	2 (<1%)	0
	>0 - 25 mm	28 (4%)	26 (4%)	23 (3%)	6 (1%)	1 (<1%)	0	1 (<1%)	0
	>25 - 50 mm	1 (<1%)	1 (<1%)	6 (1%)	2 (<1%)	3 (<1%)	0	0	0
	> 50 mm	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0
Induration (mm)	N	711	709	708	709	709	709	709	709
	ANY	19 (3%)	23 (3%)	30 (4%)	6 (1%)	3 (<1%)	0	1 (<1%)	0
	>0 - 25 mm	19 (3%)	19 (3%)	22 (3%)	4 (1%)	2 (<1%)	0	1 (<1%)	0
	>25 - 50 mm	0	3 (<1%)	7 (1%)	2 (<1%)	1 (<1%)	0	0	0
	> 50 mm	0	1 (<1%)	1 (<1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	711	709	708	709	709	709	709	709
	ANY	0	5 (1%)	10 (1%)	5 (1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
	MILD	0	5 (1%)	7 (1%)	4 (1%)	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	MODERATE	0	0	3 (<1%)	1 (<1%)	0	0	1 (<1%)	0
	SEVERE	0	0	0	0	0	0	0	0
Nausea	N	711	709	708	709	709	709	709	709
	ANY	3 (<1%)	13 (2%)	16 (2%)	7 (1%)	2 (<1%)	2 (<1%)	2 (<1%)	0
	MILD	2 (<1%)	11 (2%)	12 (2%)	3 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0
	MODERATE	1 (<1%)	2 (<1%)	4 (1%)	4 (1%)	1 (<1%)	0	0	0
	SEVERE	0	0	0	0	0	0	1 (<1%)	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=711)	6HR (N=711)	DAY 2 (N=711)	DAY 3 (N=711)	DAY 4 (N=711)	DAY 5 (N=711)	DAY 6 (N=711)	DAY 7 (N=711)
SYSTEMIC									
Malaise	N	711	709	708	709	709	709	709	709
	ANY	0	12 (2%)	26 (4%)	9 (1%)	6 (1%)	5 (1%)	2 (<1%)	2 (<1%)
	MILD	0	9 (1%)	19 (3%)	5 (1%)	3 (<1%)	2 (<1%)	0	2 (<1%)
	MODERATE	0	3 (<1%)	6 (1%)	4 (1%)	3 (<1%)	3 (<1%)	1 (<1%)	0
	SEVERE	0	0	1 (<1%)	0	0	0	1 (<1%)	0
Myalgia	N	711	709	708	709	709	709	709	709
	ANY	1 (<1%)	18 (3%)	38 (5%)	9 (1%)	4 (1%)	9 (1%)	6 (1%)	2 (<1%)
	MILD	1 (<1%)	15 (2%)	27 (4%)	7 (1%)	3 (<1%)	7 (1%)	4 (1%)	2 (<1%)
	MODERATE	0	3 (<1%)	10 (1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0
	SEVERE	0	0	1 (<1%)	0	0	0	1 (<1%)	0
Arthralgia	N	711	709	708	709	709	709	709	709
	ANY	1 (<1%)	10 (1%)	17 (2%)	4 (1%)	4 (1%)	4 (1%)	2 (<1%)	0
	MILD	1 (<1%)	7 (1%)	12 (2%)	3 (<1%)	3 (<1%)	0	2 (<1%)	0
	MODERATE	0	2 (<1%)	5 (1%)	1 (<1%)	1 (<1%)	4 (1%)	0	0
	SEVERE	0	1 (<1%)	0	0	0	0	0	0
Headache	N	711	709	708	709	709	709	709	709
	ANY	10 (1%)	43 (6%)	49 (7%)	28 (4%)	11 (2%)	8 (1%)	12 (2%)	5 (1%)
	MILD	8 (1%)	30 (4%)	34 (5%)	21 (3%)	8 (1%)	5 (1%)	8 (1%)	3 (<1%)
	MODERATE	1 (<1%)	12 (2%)	11 (2%)	7 (1%)	1 (<1%)	3 (<1%)	4 (1%)	2 (<1%)
	SEVERE	1 (<1%)	1 (<1%)	4 (1%)	0	2 (<1%)	0	0	0
Rash	N	711	709	708	709	709	709	709	709
	ANY	1 (<1%)	4 (1%)	3 (<1%)	3 (<1%)	4 (1%)	0	1 (<1%)	0
	OTHER	0	2 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0
	URTICARIAL	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	4 (1%)	0	0	0
Fever (>= 38C)	N	709	696	704	703	700	700	697	694
	YES	0	0	3 (<1%)	0	1 (<1%)	0	1 (<1%)	0
	NO	709 (100%)	696 (100%)	701 (100%)	703 (100%)	699 (100%)	700 (100%)	696 (100%)	694 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=711)	6HR (N=711)	DAY 2 (N=711)	DAY 3 (N=711)	DAY 4 (N=711)	DAY 5 (N=711)	DAY 6 (N=711)	DAY 7 (N=711)
OTHER									
Stayed Home	N	0	708	706	708	708	707	708	708
	YES	0	1 (<1%)	6 (1%)	1 (<1%)	2 (<1%)	0	0	0
	NO	0	707 (100%)	700 (99%)	707 (100%)	706 (100%)	707 (100%)	708 (100%)	708 (100%)
Analgesic Antipyretics	N	711	709	708	709	709	709	709	707
	YES	13 (2%)	36 (5%)	57 (8%)	28 (4%)	13 (2%)	9 (1%)	11 (2%)	9 (1%)
	NO	698 (98%)	673 (95%)	651 (92%)	681 (96%)	696 (98%)	700 (99%)	698 (98%)	698 (99%)
Temperature (C)	N	709	696	704	703	700	700	697	694
	<38 C	709 (100%)	696 (100%)	701 (100%)	703 (100%)	699 (100%)	700 (100%)	696 (100%)	694 (100%)
	38 - 38.9 C	0	0	3 (<1%)	0	1 (<1%)	0	1 (<1%)	0
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=231)	6HR (N=231)	DAY 2 (N=231)	DAY 3 (N=231)	DAY 4 (N=231)	DAY 5 (N=231)	DAY 6 (N=231)	DAY 7 (N=231)
INJECTION SITE									
Pain	N	231	230	229	229	229	229	229	229
	ANY	28 (12%)	30 (13%)	28 (12%)	4 (2%)	1 (<1%)	1 (<1%)	0	0
	MILD	28 (12%)	27 (12%)	26 (11%)	4 (2%)	1 (<1%)	1 (<1%)	0	0
	MODERATE	0	3 (1%)	2 (1%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	231	230	229	229	229	229	229	229
	ANY	10 (4%)	9 (4%)	9 (4%)	5 (2%)	0	1 (<1%)	0	0
	>0 - 25 mm	10 (4%)	9 (4%)	7 (3%)	5 (2%)	0	1 (<1%)	0	0
	>25 - 50 mm	0	0	2 (1%)	0	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	231	230	229	229	229	229	229	229
	ANY	6 (3%)	3 (1%)	8 (3%)	5 (2%)	0	1 (<1%)	0	0
	>0 - 25 mm	6 (3%)	3 (1%)	7 (3%)	4 (2%)	0	1 (<1%)	0	0
	>25 - 50 mm	0	0	1 (<1%)	1 (<1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
SYSTEMIC									
Chills	N	231	230	229	229	229	229	229	229
	ANY	0	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)	0	0	0
	MILD	0	1 (<1%)	2 (1%)	1 (<1%)	0	0	0	0
	MODERATE	0	0	0	0	1 (<1%)	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Nausea	N	231	230	229	229	229	229	229	229
	ANY	0	3 (1%)	1 (<1%)	2 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
	MILD	0	3 (1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)
	MODERATE	0	0	0	0	1 (<1%)	0	0	0
	SEVERE	0	0	0	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=231)	6HR (N=231)	DAY 2 (N=231)	DAY 3 (N=231)	DAY 4 (N=231)	DAY 5 (N=231)	DAY 6 (N=231)	DAY 7 (N=231)
SYSTEMIC									
Malaise	N	231	230	229	229	229	229	229	229
	ANY	0	2 (1%)	7 (3%)	5 (2%)	1 (<1%)	3 (1%)	1 (<1%)	0
	MILD	0	1 (<1%)	7 (3%)	3 (1%)	1 (<1%)	2 (1%)	1 (<1%)	0
	MODERATE	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	0
	SEVERE	0	0	0	1 (<1%)	0	0	0	0
Myalgia	N	231	230	229	229	229	229	229	229
	ANY	1 (<1%)	6 (3%)	11 (5%)	5 (2%)	3 (1%)	3 (1%)	0	0
	MILD	1 (<1%)	6 (3%)	10 (4%)	2 (1%)	3 (1%)	2 (1%)	0	0
	MODERATE	0	0	0	2 (1%)	0	1 (<1%)	0	0
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Arthralgia	N	231	230	228	229	229	229	229	229
	ANY	0	2 (1%)	5 (2%)	6 (3%)	1 (<1%)	0	0	0
	MILD	0	2 (1%)	4 (2%)	4 (2%)	1 (<1%)	0	0	0
	MODERATE	0	0	1 (<1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	1 (<1%)	0	0	0	0
Headache	N	231	230	229	229	229	229	229	229
	ANY	4 (2%)	14 (6%)	17 (7%)	9 (4%)	5 (2%)	4 (2%)	4 (2%)	4 (2%)
	MILD	4 (2%)	12 (5%)	14 (6%)	5 (2%)	3 (1%)	1 (<1%)	4 (2%)	3 (1%)
	MODERATE	0	2 (1%)	3 (1%)	4 (2%)	2 (1%)	2 (1%)	0	1 (<1%)
	SEVERE	0	0	0	0	0	1 (<1%)	0	0
Rash	N	231	230	229	229	229	229	229	229
	ANY	0	0	0	1 (<1%)	0	0	0	1 (<1%)
	OTHER	0	0	0	1 (<1%)	0	0	0	1 (<1%)
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	230	224	228	226	227	228	226	223
	YES	0	0	0	0	0	0	0	0
	NO	230 (100%)	224 (100%)	228 (100%)	226 (100%)	227 (100%)	228 (100%)	226 (100%)	223 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=231)	6HR (N=231)	DAY 2 (N=231)	DAY 3 (N=231)	DAY 4 (N=231)	DAY 5 (N=231)	DAY 6 (N=231)	DAY 7 (N=231)
OTHER									
Stayed Home	N	0	230	230	230	230	230	229	230
	YES	0	0	0	0	0	0	0	0
	NO	0	230 (100%)	230 (100%)	230 (100%)	230 (100%)	230 (100%)	229 (100%)	230 (100%)
Analgesic Antipyretics	N	231	230	229	229	229	229	229	229
	YES	6 (3%)	12 (5%)	13 (6%)	11 (5%)	3 (1%)	5 (2%)	2 (1%)	3 (1%)
	NO	225 (97%)	218 (95%)	216 (94%)	218 (95%)	226 (99%)	224 (98%)	227 (99%)	226 (99%)
Temperature (C)	N	230	224	228	226	227	228	226	223
	<38 C	230 (100%)	224 (100%)	228 (100%)	226 (100%)	227 (100%)	228 (100%)	226 (100%)	223 (100%)
	38 - 38.9 C	0	0	0	0	0	0	0	0
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=750)	6HR (N=750)	DAY 2 (N=750)	DAY 3 (N=750)	DAY 4 (N=750)	DAY 5 (N=750)	DAY 6 (N=750)	DAY 7 (N=750)
INJECTION SITE									
Pain	N	750	723	749	750	748	747	746	744
	ANY	129 (17%)	69 (10%)	43 (6%)	17 (2%)	2 (<1%)	4 (1%)	5 (1%)	4 (1%)
	MILD	103 (14%)	50 (7%)	31 (4%)	11 (1%)	1 (<1%)	3 (<1%)	5 (1%)	2 (<1%)
	MODERATE	25 (3%)	17 (2%)	8 (1%)	5 (1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	4 (1%)	1 (<1%)	0	0	0	1 (<1%)
Erythema (mm)	N	750	720	743	745	744	743	743	741
	ANY	42 (6%)	14 (2%)	13 (2%)	4 (1%)	2 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)
	>0 - 25 mm	41 (5%)	10 (1%)	10 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
	>25 - 50 mm	1 (<1%)	4 (1%)	2 (<1%)	0	0	1 (<1%)	1 (<1%)	0
	> 50 mm	0	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Induration (mm)	N	750	721	744	745	743	743	742	740
	ANY	36 (5%)	12 (2%)	15 (2%)	3 (<1%)	2 (<1%)	2 (<1%)	4 (1%)	1 (<1%)
	>0 - 25 mm	36 (5%)	9 (1%)	13 (2%)	3 (<1%)	2 (<1%)	2 (<1%)	4 (1%)	0
	>25 - 50 mm	0	2 (<1%)	1 (<1%)	0	0	0	0	0
	> 50 mm	0	1 (<1%)	1 (<1%)	0	0	0	0	1 (<1%)
SYSTEMIC									
Chills	N	750	724	749	749	748	748	748	746
	ANY	1 (<1%)	18 (2%)	15 (2%)	7 (1%)	6 (1%)	4 (1%)	4 (1%)	4 (1%)
	MILD	1 (<1%)	12 (2%)	6 (1%)	7 (1%)	3 (<1%)	4 (1%)	1 (<1%)	2 (<1%)
	MODERATE	0	4 (1%)	8 (1%)	0	2 (<1%)	0	2 (<1%)	2 (<1%)
	SEVERE	0	2 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Nausea	N	750	724	749	749	748	748	748	746
	ANY	2 (<1%)	8 (1%)	10 (1%)	9 (1%)	6 (1%)	5 (1%)	2 (<1%)	1 (<1%)
	MILD	2 (<1%)	8 (1%)	8 (1%)	7 (1%)	5 (1%)	4 (1%)	1 (<1%)	0
	MODERATE	0	0	1 (<1%)	2 (<1%)	0	1 (<1%)	0	0
	SEVERE	0	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=750)	6HR (N=750)	DAY 2 (N=750)	DAY 3 (N=750)	DAY 4 (N=750)	DAY 5 (N=750)	DAY 6 (N=750)	DAY 7 (N=750)
SYSTEMIC									
Malaise	N	750	724	749	749	748	748	748	746
	ANY	11 (1%)	33 (5%)	43 (6%)	26 (3%)	12 (2%)	5 (1%)	8 (1%)	6 (1%)
	MILD	9 (1%)	24 (3%)	26 (3%)	17 (2%)	6 (1%)	4 (1%)	5 (1%)	3 (<1%)
	MODERATE	1 (<1%)	6 (1%)	15 (2%)	8 (1%)	4 (1%)	1 (<1%)	1 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	1 (<1%)
Myalgia	N	750	725	749	749	748	748	748	746
	ANY	8 (1%)	23 (3%)	26 (3%)	15 (2%)	8 (1%)	3 (<1%)	3 (<1%)	6 (1%)
	MILD	7 (1%)	17 (2%)	15 (2%)	4 (1%)	6 (1%)	2 (<1%)	2 (<1%)	4 (1%)
	MODERATE	0	4 (1%)	8 (1%)	11 (1%)	1 (<1%)	1 (<1%)	0	2 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Arthralgia	N	750	724	749	749	748	748	748	746
	ANY	6 (1%)	8 (1%)	22 (3%)	12 (2%)	7 (1%)	3 (<1%)	1 (<1%)	3 (<1%)
	MILD	5 (1%)	6 (1%)	14 (2%)	9 (1%)	2 (<1%)	3 (<1%)	0	2 (<1%)
	MODERATE	0	0	5 (1%)	3 (<1%)	4 (1%)	0	0	1 (<1%)
	SEVERE	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Headache	N	750	725	749	749	748	748	748	747
	ANY	31 (4%)	50 (7%)	44 (6%)	30 (4%)	15 (2%)	10 (1%)	8 (1%)	4 (1%)
	MILD	29 (4%)	38 (5%)	27 (4%)	20 (3%)	10 (1%)	3 (<1%)	5 (1%)	3 (<1%)
	MODERATE	1 (<1%)	7 (1%)	12 (2%)	9 (1%)	2 (<1%)	4 (1%)	3 (<1%)	1 (<1%)
	SEVERE	1 (<1%)	5 (1%)	5 (1%)	1 (<1%)	3 (<1%)	3 (<1%)	0	0
Rash	N	750	724	749	749	748	748	748	746
	ANY	1 (<1%)	3 (<1%)	4 (1%)	7 (1%)	2 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
	OTHER	0	1 (<1%)	0	3 (<1%)	1 (<1%)	0	0	0
	URTICARIAL	1 (<1%)	2 (<1%)	4 (1%)	4 (1%)	1 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
Fever (>= 38C)	N	749	665	686	683	675	668	666	652
	YES	1 (<1%)	6 (1%)	10 (1%)	1 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)	4 (1%)
	NO	748 (100%)	659 (99%)	676 (99%)	682 (100%)	672 (100%)	667 (100%)	663 (100%)	648 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=750)	6HR (N=750)	DAY 2 (N=750)	DAY 3 (N=750)	DAY 4 (N=750)	DAY 5 (N=750)	DAY 6 (N=750)	DAY 7 (N=750)
OTHER									
Stayed Home	N	0	722	743	745	744	744	743	741
	YES	0	11 (2%)	11 (1%)	7 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	NO	0	711 (98%)	732 (99%)	738 (99%)	743 (100%)	743 (100%)	741 (100%)	739 (100%)
Analgesic Antipyretics	N	750	722	743	745	743	743	742	740
	YES	3 (<1%)	32 (4%)	30 (4%)	17 (2%)	6 (1%)	9 (1%)	5 (1%)	4 (1%)
	NO	747 (100%)	690 (96%)	713 (96%)	728 (98%)	737 (99%)	734 (99%)	737 (99%)	736 (99%)
Temperature (C)	N	749	665	686	683	675	668	666	652
	<38 C	748 (100%)	659 (99%)	676 (99%)	682 (100%)	672 (100%)	667 (100%)	663 (100%)	648 (99%)
	38 - 38.9 C	1 (<1%)	5 (1%)	8 (1%)	1 (<1%)	2 (<1%)	0	3 (<1%)	4 (1%)
	39.0 - 39.9 C	0	1 (<1%)	2 (<1%)	0	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	1 (<1%)	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=418)	6HR (N=418)	DAY 2 (N=418)	DAY 3 (N=418)	DAY 4 (N=418)	DAY 5 (N=418)	DAY 6 (N=418)	DAY 7 (N=418)
INJECTION SITE									
Pain	N	418	402	413	411	414	414	414	411
	ANY	66 (16%)	50 (12%)	30 (7%)	11 (3%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	MILD	56 (13%)	41 (10%)	21 (5%)	10 (2%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	MODERATE	10 (2%)	7 (2%)	7 (2%)	1 (<1%)	0	0	0	0
	SEVERE	0	2 (<1%)	2 (<1%)	0	0	0	0	0
Erythema (mm)	N	418	402	414	412	414	414	414	412
	ANY	30 (7%)	5 (1%)	6 (1%)	4 (1%)	1 (<1%)	2 (<1%)	0	0
	>0 - 25 mm	30 (7%)	5 (1%)	5 (1%)	3 (1%)	1 (<1%)	2 (<1%)	0	0
	>25 - 50 mm	0	0	1 (<1%)	1 (<1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	418	402	414	412	414	414	414	412
	ANY	31 (7%)	9 (2%)	9 (2%)	5 (1%)	0	0	0	0
	>0 - 25 mm	30 (7%)	7 (2%)	9 (2%)	2 (<1%)	0	0	0	0
	>25 - 50 mm	1 (<1%)	1 (<1%)	0	3 (1%)	0	0	0	0
	> 50 mm	0	1 (<1%)	0	0	0	0	0	0
SYSTEMIC									
Chills	N	418	402	414	412	413	414	414	412
	ANY	1 (<1%)	7 (2%)	11 (3%)	3 (1%)	4 (1%)	3 (1%)	1 (<1%)	1 (<1%)
	MILD	1 (<1%)	5 (1%)	7 (2%)	2 (<1%)	2 (<1%)	3 (1%)	0	1 (<1%)
	MODERATE	0	2 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	0	1 (<1%)	0
	SEVERE	0	0	2 (<1%)	0	0	0	0	0
Nausea	N	418	402	414	412	413	414	414	412
	ANY	5 (1%)	6 (1%)	7 (2%)	6 (1%)	6 (1%)	3 (1%)	1 (<1%)	0
	MILD	4 (1%)	4 (1%)	6 (1%)	6 (1%)	4 (1%)	1 (<1%)	1 (<1%)	0
	MODERATE	1 (<1%)	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)	0	0
	SEVERE	0	1 (<1%)	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=418)	6HR (N=418)	DAY 2 (N=418)	DAY 3 (N=418)	DAY 4 (N=418)	DAY 5 (N=418)	DAY 6 (N=418)	DAY 7 (N=418)
SYSTEMIC									
Malaise	N	418	402	414	412	413	414	414	412
	ANY	9 (2%)	24 (6%)	25 (6%)	11 (3%)	6 (1%)	4 (1%)	3 (1%)	0
	MILD	7 (2%)	18 (4%)	17 (4%)	6 (1%)	4 (1%)	4 (1%)	1 (<1%)	0
	MODERATE	2 (<1%)	6 (1%)	6 (1%)	4 (1%)	1 (<1%)	0	2 (<1%)	0
	SEVERE	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Myalgia	N	418	402	414	412	413	414	414	412
	ANY	5 (1%)	16 (4%)	20 (5%)	11 (3%)	3 (1%)	8 (2%)	4 (1%)	1 (<1%)
	MILD	5 (1%)	12 (3%)	12 (3%)	7 (2%)	2 (<1%)	5 (1%)	3 (1%)	1 (<1%)
	MODERATE	0	4 (1%)	6 (1%)	4 (1%)	0	2 (<1%)	1 (<1%)	0
	SEVERE	0	0	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Arthralgia	N	418	402	414	412	413	414	414	412
	ANY	3 (1%)	7 (2%)	12 (3%)	7 (2%)	4 (1%)	4 (1%)	1 (<1%)	2 (<1%)
	MILD	3 (1%)	4 (1%)	7 (2%)	3 (1%)	2 (<1%)	4 (1%)	1 (<1%)	2 (<1%)
	MODERATE	0	3 (1%)	3 (1%)	3 (1%)	1 (<1%)	0	0	0
	SEVERE	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Headache	N	418	402	414	412	413	414	414	412
	ANY	16 (4%)	28 (7%)	31 (7%)	20 (5%)	12 (3%)	3 (1%)	7 (2%)	2 (<1%)
	MILD	14 (3%)	21 (5%)	21 (5%)	13 (3%)	4 (1%)	2 (<1%)	7 (2%)	1 (<1%)
	MODERATE	2 (<1%)	5 (1%)	8 (2%)	5 (1%)	5 (1%)	1 (<1%)	0	1 (<1%)
	SEVERE	0	2 (<1%)	2 (<1%)	2 (<1%)	3 (1%)	0	0	0
Rash	N	418	402	414	412	413	414	414	412
	ANY	0	3 (1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
	OTHER	0	0	1 (<1%)	1 (<1%)	0	0	0	0
	URTICARIAL	0	3 (1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Fever (>= 38C)	N	418	364	373	367	370	367	362	354
	YES	1 (<1%)	1 (<1%)	4 (1%)	5 (1%)	2 (1%)	0	0	2 (1%)
	NO	417 (100%)	363 (100%)	369 (99%)	362 (99%)	368 (99%)	367 (100%)	362 (100%)	352 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 27

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs. Controls by Study within Age Group

Reaction		Number (%) of Subjects							
		30M (N=418)	6HR (N=418)	DAY 2 (N=418)	DAY 3 (N=418)	DAY 4 (N=418)	DAY 5 (N=418)	DAY 6 (N=418)	DAY 7 (N=418)
OTHER									
Stayed Home	N	0	402	413	411	414	415	415	413
	YES	0	7 (2%)	9 (2%)	1 (<1%)	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
	NO	0	395 (98%)	404 (98%)	410 (100%)	412 (100%)	412 (99%)	414 (100%)	412 (100%)
Analgesic Antipyretics	N	417	400	411	410	413	415	415	413
	YES	1 (<1%)	20 (5%)	29 (7%)	18 (4%)	5 (1%)	4 (1%)	5 (1%)	0
	NO	416 (100%)	380 (95%)	382 (93%)	392 (96%)	408 (99%)	411 (99%)	410 (99%)	413 (100%)
Temperature (C)	N	418	364	373	367	370	367	362	354
	<38 C	417 (100%)	363 (100%)	369 (99%)	362 (99%)	368 (99%)	367 (100%)	362 (100%)	352 (99%)
	38 - 38.9 C	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)	1 (<1%)	0	0	2 (1%)
	39.0 - 39.9 C	0	0	2 (1%)	1 (<1%)	1 (<1%)	0	0	0
	>= 40 C	0	0	1 (<1%)	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONTROL.SAS(WARTERO) 10JUL08, 08:31 SAS.9.1 - PINJONSET_MEN_VS_CONTROL

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Group: P6 ACWY

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
INJECTION SITE									
Pain	N	151	150	150	150	149	150	149	149
	ANY	26 (17%)	31 (21%)	21 (14%)	3 (2%)	0	0	0	0
	MILD	23 (15%)	29 (19%)	19 (13%)	3 (2%)	0	0	0	0
	MODERATE	3 (2%)	2 (1%)	2 (1%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	151	148	148	148	147	148	148	147
	ANY	48 (32%)	2 (1%)	5 (3%)	2 (1%)	0	0	0	0
	>0 - 25 mm	45 (30%)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0
	>25 - 50 mm	3 (2%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	1 (1%)	3 (2%)	1 (1%)	0	0	0	0
Induration (mm)	N	151	149	149	149	148	149	149	148
	ANY	22 (15%)	3 (2%)	8 (5%)	1 (1%)	0	0	0	0
	>0 - 25 mm	20 (13%)	3 (2%)	4 (3%)	0	0	0	0	0
	>25 - 50 mm	2 (1%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	0	3 (2%)	1 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	12 (8%)	1 (1%)	5 (3%)	0	1 (1%)	2 (1%)
	MILD	0	2 (1%)	8 (5%)	1 (1%)	4 (3%)	0	1 (1%)	1 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	2 (1%)	0	0	0	0	0
Nausea	N	151	150	150	150	149	150	150	149
	ANY	2 (1%)	5 (3%)	8 (5%)	1 (1%)	2 (1%)	0	0	4 (3%)
	MILD	2 (1%)	4 (3%)	6 (4%)	0	1 (1%)	0	0	2 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	0	1 (1%)	0	0	0	1 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Group: P6 ACWY

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
SYSTEMIC									
Malaise	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	0	13 (9%)	1 (1%)	2 (1%)	0	4 (3%)	2 (1%)
	MILD	1 (1%)	0	9 (6%)	0	1 (1%)	0	2 (1%)	1 (1%)
	MODERATE	0	0	2 (1%)	0	1 (1%)	0	2 (1%)	1 (1%)
	SEVERE	0	0	2 (1%)	1 (1%)	0	0	0	0
Myalgia	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	14 (9%)	7 (5%)	8 (5%)	3 (2%)	1 (1%)	1 (1%)	0
	MILD	1 (1%)	12 (8%)	3 (2%)	8 (5%)	2 (1%)	1 (1%)	1 (1%)	0
	MODERATE	0	2 (1%)	3 (2%)	0	1 (1%)	0	0	0
	SEVERE	0	0	1 (1%)	0	0	0	0	0
Arthralgia	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MILD	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MODERATE	0	0	0	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	151	150	150	150	149	150	150	149
	ANY	11 (7%)	9 (6%)	24 (16%)	3 (2%)	3 (2%)	3 (2%)	6 (4%)	3 (2%)
	MILD	11 (7%)	9 (6%)	16 (11%)	1 (1%)	2 (1%)	3 (2%)	5 (3%)	2 (1%)
	MODERATE	0	0	5 (3%)	1 (1%)	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	3 (2%)	1 (1%)	0	0	1 (1%)	0
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	151	149	149	146	144	146	147	148
	YES	0	0	0	0	0	0	0	1 (1%)
	NO	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
OTHER									
Stayed Home	N	0	150	149	149	148	149	148	148
	YES	0	0	4 (3%)	1 (1%)	0	0	1 (1%)	0
	NO	0	150 (100%)	145 (97%)	148 (99%)	148 (100%)	149 (100%)	147 (99%)	148 (100%)
Analgesic Antipyretics	N	151	150	149	149	148	149	148	148
	YES	2 (1%)	7 (5%)	15 (10%)	3 (2%)	4 (3%)	2 (1%)	3 (2%)	3 (2%)
	NO	149 (99%)	143 (95%)	134 (90%)	146 (98%)	144 (97%)	147 (99%)	145 (98%)	145 (98%)
Temperature (C)	N	151	149	149	146	144	146	147	148
	<38 C	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)
	38 - 38.9 C	0	0	0	0	0	0	0	1 (1%)
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
INJECTION SITE									
Pain	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	67 (19%)	28 (8%)	10 (3%)	1 (<1%)	1 (<1%)	0	0
	MILD	6 (2%)	51 (14%)	24 (7%)	8 (2%)	0	1 (<1%)	0	0
	MODERATE	3 (1%)	12 (3%)	3 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	0	4 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	40 (11%)	11 (3%)	6 (2%)	0	0	0	0
	>0 - 25 mm	9 (3%)	40 (11%)	9 (3%)	3 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	357	357	357	357	357	357	357	357
	ANY	5 (1%)	29 (8%)	17 (5%)	7 (2%)	0	0	0	1 (<1%)
	>0 - 25 mm	5 (1%)	28 (8%)	15 (4%)	4 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	1 (<1%)
	> 50 mm	0	1 (<1%)	0	0	0	0	0	0
SYSTEMIC									
Chills	N	357	357	357	357	357	357	357	357
	ANY	0	21 (6%)	7 (2%)	6 (2%)	3 (1%)	5 (1%)	2 (1%)	3 (1%)
	MILD	0	14 (4%)	5 (1%)	3 (1%)	0	3 (1%)	2 (1%)	3 (1%)
	MODERATE	0	5 (1%)	2 (1%)	2 (1%)	2 (1%)	2 (1%)	0	0
	SEVERE	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0	0
Nausea	N	357	357	357	357	357	357	357	357
	ANY	0	8 (2%)	9 (3%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	3 (1%)
	MILD	0	6 (2%)	7 (2%)	2 (1%)	1 (<1%)	0	2 (1%)	3 (1%)
	MODERATE	0	2 (1%)	2 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	0	0	2 (1%)	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
SYSTEMIC									
Malaise	N	357	357	357	357	357	357	357	357
	ANY	0	24 (7%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)	0	2 (1%)
	MILD	0	17 (5%)	3 (1%)	4 (1%)	2 (1%)	1 (<1%)	0	1 (<1%)
	MODERATE	0	7 (2%)	4 (1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)
	SEVERE	0	0	0	1 (<1%)	0	0	0	0
Myalgia	N	357	357	357	357	357	357	357	357
	ANY	0	46 (13%)	18 (5%)	10 (3%)	2 (1%)	2 (1%)	1 (<1%)	0
	MILD	0	33 (9%)	12 (3%)	7 (2%)	2 (1%)	2 (1%)	0	0
	MODERATE	0	10 (3%)	6 (2%)	2 (1%)	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	0	1 (<1%)	0	0	0	0
Arthralgia	N	357	357	357	357	357	357	357	357
	ANY	0	23 (6%)	8 (2%)	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)	2 (1%)
	MILD	0	15 (4%)	5 (1%)	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
	MODERATE	0	5 (1%)	2 (1%)	0	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Headache	N	357	357	357	357	357	357	357	357
	ANY	3 (1%)	64 (18%)	29 (8%)	10 (3%)	6 (2%)	9 (3%)	4 (1%)	3 (1%)
	MILD	3 (1%)	45 (13%)	21 (6%)	9 (3%)	5 (1%)	6 (2%)	3 (1%)	2 (1%)
	MODERATE	0	13 (4%)	5 (1%)	1 (<1%)	0	3 (1%)	0	0
	SEVERE	0	6 (2%)	3 (1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	357	356	356	357	356	355	355	353
	YES	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	3 (1%)	2 (1%)	0
	NO	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
OTHER									
Stayed Home	N	0	357	357	357	357	357	357	356
	YES	0	1 (<1%)	4 (1%)	3 (1%)	2 (1%)	2 (1%)	0	0
	NO	0	356 (100%)	353 (99%)	354 (99%)	355 (99%)	355 (99%)	357 (100%)	356 (100%)
Analgesic Antipyretics	N	357	357	357	357	357	357	357	356
	YES	0	6 (2%)	8 (2%)	5 (1%)	4 (1%)	3 (1%)	2 (1%)	3 (1%)
	NO	357 (100%)	351 (98%)	349 (98%)	352 (99%)	353 (99%)	354 (99%)	355 (99%)	353 (99%)
Temperature (C)	N	357	356	356	357	356	355	355	353
	<38 C	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)
	38 - 38.9 C	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	0
	39.0 - 39.9 C	0	0	0	0	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	0	0	0	0

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=359)	6HR (N=359)	DAY 2 (N=359)	DAY 3 (N=359)	DAY 4 (N=359)	DAY 5 (N=359)	DAY 6 (N=359)	DAY 7 (N=359)
INJECTION SITE									
Pain	N	359	358	358	358	358	358	358	358
	ANY	3 (1%)	57 (16%)	16 (4%)	4 (1%)	1 (<1%)	0	1 (<1%)	0
	MILD	3 (1%)	37 (10%)	11 (3%)	4 (1%)	1 (<1%)	0	1 (<1%)	0
	MODERATE	0	20 (6%)	4 (1%)	0	0	0	0	0
	SEVERE	0	0	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	359	358	358	358	358	358	358	358
	ANY	5 (1%)	28 (8%)	7 (2%)	6 (2%)	2 (1%)	0	0	0
	>0 - 25 mm	5 (1%)	27 (8%)	6 (2%)	4 (1%)	2 (1%)	0	0	0
	>25 - 50 mm	0	1 (<1%)	1 (<1%)	2 (1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	359	358	358	358	358	358	358	357
	ANY	1 (<1%)	22 (6%)	9 (3%)	5 (1%)	2 (1%)	2 (1%)	0	0
	>0 - 25 mm	1 (<1%)	19 (5%)	5 (1%)	3 (1%)	2 (1%)	1 (<1%)	0	0
	>25 - 50 mm	0	3 (1%)	4 (1%)	2 (1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	1 (<1%)	0	0
SYSTEMIC									
Chills	N	359	358	358	358	358	358	358	358
	ANY	0	21 (6%)	8 (2%)	4 (1%)	2 (1%)	2 (1%)	0	2 (1%)
	MILD	0	19 (5%)	4 (1%)	3 (1%)	1 (<1%)	2 (1%)	0	2 (1%)
	MODERATE	0	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	0	0	2 (1%)	0	0	0	0	0
Nausea	N	359	358	358	358	358	358	358	358
	ANY	0	18 (5%)	11 (3%)	7 (2%)	3 (1%)	0	2 (1%)	2 (1%)
	MILD	0	16 (4%)	8 (2%)	4 (1%)	2 (1%)	0	2 (1%)	2 (1%)
	MODERATE	0	1 (<1%)	1 (<1%)	2 (1%)	0	0	0	0
	SEVERE	0	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Group: P11 ACWY+Tdap

Reaction		Number (%) of Subjects							
		30M (N=359)	6HR (N=359)	DAY 2 (N=359)	DAY 3 (N=359)	DAY 4 (N=359)	DAY 5 (N=359)	DAY 6 (N=359)	DAY 7 (N=359)
SYSTEMIC									
Malaise	N	359	358	358	358	358	358	358	358
	ANY	1 (<1%)	33 (9%)	21 (6%)	5 (1%)	3 (1%)	0	1 (<1%)	1 (<1%)
	MILD	1 (<1%)	27 (8%)	11 (3%)	0	3 (1%)	0	1 (<1%)	1 (<1%)
	MODERATE	0	4 (1%)	7 (2%)	4 (1%)	0	0	0	0
	SEVERE	0	2 (1%)	3 (1%)	1 (<1%)	0	0	0	0
Myalgia	N	359	358	358	358	358	358	358	358
	ANY	2 (1%)	86 (24%)	23 (6%)	6 (2%)	0	1 (<1%)	0	0
	MILD	0	51 (14%)	16 (4%)	4 (1%)	0	1 (<1%)	0	0
	MODERATE	2 (1%)	28 (8%)	5 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	7 (2%)	2 (1%)	1 (<1%)	0	0	0	0
Arthralgia	N	359	358	358	358	358	358	358	358
	ANY	1 (<1%)	40 (11%)	11 (3%)	3 (1%)	0	0	2 (1%)	0
	MILD	0	22 (6%)	7 (2%)	1 (<1%)	0	0	2 (1%)	0
	MODERATE	1 (<1%)	15 (4%)	2 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	3 (1%)	2 (1%)	1 (<1%)	0	0	0	0
Headache	N	359	358	358	358	358	358	358	358
	ANY	3 (1%)	65 (18%)	27 (8%)	17 (5%)	7 (2%)	5 (1%)	4 (1%)	1 (<1%)
	MILD	2 (1%)	50 (14%)	14 (4%)	10 (3%)	3 (1%)	5 (1%)	3 (1%)	1 (<1%)
	MODERATE	1 (<1%)	13 (4%)	9 (3%)	4 (1%)	2 (1%)	0	0	0
	SEVERE	0	2 (1%)	4 (1%)	3 (1%)	2 (1%)	0	1 (<1%)	0
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0
Fever (>= 38C)	N	359	358	358	358	357	357	357	357
	YES	0	0	7 (2%)	3 (1%)	0	0	0	1 (<1%)
	NO	359 (100%)	358 (100%)	351 (98%)	355 (99%)	357 (100%)	357 (100%)	357 (100%)	356 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Group: P11 ACWY+Tdap

Reaction		Number (%) of Subjects							
		30M (N=359)	6HR (N=359)	DAY 2 (N=359)	DAY 3 (N=359)	DAY 4 (N=359)	DAY 5 (N=359)	DAY 6 (N=359)	DAY 7 (N=359)
OTHER									
Stayed Home	N	0	358	358	358	358	358	358	358
	YES	0	1 (<1%)	6 (2%)	3 (1%)	0	0	2 (1%)	0
	NO	0	357 (100%)	352 (98%)	355 (99%)	358 (100%)	358 (100%)	356 (99%)	358 (100%)
Analgesic Antipyretics	N	359	358	358	358	358	358	358	358
	YES	2 (1%)	6 (2%)	19 (5%)	3 (1%)	3 (1%)	3 (1%)	1 (<1%)	1 (<1%)
	NO	357 (99%)	352 (98%)	339 (95%)	355 (99%)	355 (99%)	355 (99%)	357 (100%)	357 (100%)
Temperature (C)	N	359	358	358	358	357	357	357	357
	<38 C	359 (100%)	358 (100%)	351 (98%)	355 (99%)	357 (100%)	357 (100%)	357 (100%)	356 (100%)
	38 - 38.9 C	0	0	6 (2%)	3 (1%)	0	0	0	0
	39.0 - 39.9 C	0	0	1 (<1%)	0	0	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
INJECTION SITE									
Pain	N	1622	1607	1610	1610	1609	1607	1609	1607
	ANY	212 (13%)	296 (18%)	145 (9%)	44 (3%)	9 (1%)	7 (<1%)	0	1 (<1%)
	MILD	197 (12%)	260 (16%)	120 (7%)	43 (3%)	6 (<1%)	7 (<1%)	0	1 (<1%)
	MODERATE	14 (1%)	35 (2%)	22 (1%)	1 (<1%)	2 (<1%)	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	3 (<1%)	0	1 (<1%)	0	0	0
Erythema (mm)	N	1623	1607	1611	1611	1610	1610	1609	1608
	ANY	64 (4%)	57 (4%)	80 (5%)	34 (2%)	6 (<1%)	4 (<1%)	2 (<1%)	0
	>0 - 25 mm	61 (4%)	53 (3%)	56 (3%)	20 (1%)	4 (<1%)	3 (<1%)	2 (<1%)	0
	>25 - 50 mm	3 (<1%)	1 (<1%)	13 (1%)	9 (1%)	2 (<1%)	1 (<1%)	0	0
	> 50 mm	0	3 (<1%)	11 (1%)	5 (<1%)	0	0	0	0
Induration (mm)	N	1623	1607	1611	1610	1610	1610	1609	1608
	ANY	34 (2%)	55 (3%)	76 (5%)	26 (2%)	1 (<1%)	2 (<1%)	2 (<1%)	0
	>0 - 25 mm	34 (2%)	45 (3%)	53 (3%)	12 (1%)	0	2 (<1%)	2 (<1%)	0
	>25 - 50 mm	0	7 (<1%)	13 (1%)	9 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	3 (<1%)	10 (1%)	5 (<1%)	0	0	0	0
SYSTEMIC									
Chills	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	18 (1%)	27 (2%)	49 (3%)	13 (1%)	6 (<1%)	9 (1%)	1 (<1%)	4 (<1%)
	MILD	16 (1%)	24 (1%)	31 (2%)	10 (1%)	6 (<1%)	4 (<1%)	1 (<1%)	0
	MODERATE	2 (<1%)	1 (<1%)	15 (1%)	3 (<1%)	0	5 (<1%)	0	3 (<1%)
	SEVERE	0	2 (<1%)	3 (<1%)	0	0	0	0	1 (<1%)
Nausea	N	1625	1610	1613	1613	1612	1612	1612	1610
	ANY	14 (1%)	41 (3%)	62 (4%)	26 (2%)	16 (1%)	11 (1%)	9 (1%)	8 (<1%)
	MILD	12 (1%)	36 (2%)	42 (3%)	16 (1%)	12 (1%)	7 (<1%)	6 (<1%)	4 (<1%)
	MODERATE	2 (<1%)	5 (<1%)	17 (1%)	7 (<1%)	4 (<1%)	4 (<1%)	1 (<1%)	4 (<1%)
	SEVERE	0	0	3 (<1%)	3 (<1%)	0	0	2 (<1%)	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
SYSTEMIC									
Malaise	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	17 (1%)	33 (2%)	71 (4%)	26 (2%)	8 (<1%)	7 (<1%)	9 (1%)	6 (<1%)
	MILD	15 (1%)	25 (2%)	39 (2%)	16 (1%)	7 (<1%)	4 (<1%)	6 (<1%)	3 (<1%)
	MODERATE	2 (<1%)	8 (<1%)	23 (1%)	9 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	0	0	9 (1%)	1 (<1%)	0	1 (<1%)	0	0
Myalgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	31 (2%)	112 (7%)	102 (6%)	31 (2%)	6 (<1%)	15 (1%)	6 (<1%)	7 (<1%)
	MILD	28 (2%)	95 (6%)	74 (5%)	24 (1%)	6 (<1%)	14 (1%)	2 (<1%)	4 (<1%)
	MODERATE	1 (<1%)	14 (1%)	20 (1%)	7 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	2 (<1%)	3 (<1%)	8 (<1%)	0	0	0	1 (<1%)	0
Arthralgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	9 (1%)	25 (2%)	53 (3%)	20 (1%)	7 (<1%)	13 (1%)	4 (<1%)	6 (<1%)
	MILD	9 (1%)	22 (1%)	41 (3%)	19 (1%)	5 (<1%)	9 (1%)	2 (<1%)	5 (<1%)
	MODERATE	0	2 (<1%)	8 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	4 (<1%)	0	0	1 (<1%)	0	0
Headache	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	63 (4%)	131 (8%)	134 (8%)	44 (3%)	41 (3%)	27 (2%)	26 (2%)	12 (1%)
	MILD	57 (4%)	102 (6%)	99 (6%)	31 (2%)	33 (2%)	21 (1%)	20 (1%)	8 (<1%)
	MODERATE	5 (<1%)	25 (2%)	29 (2%)	12 (1%)	7 (<1%)	5 (<1%)	3 (<1%)	4 (<1%)
	SEVERE	1 (<1%)	4 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
Rash	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	0	4 (<1%)	15 (1%)	9 (1%)	4 (<1%)	6 (<1%)	3 (<1%)	3 (<1%)
	OTHER	0	3 (<1%)	4 (<1%)	7 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	URTICARIAL	0	1 (<1%)	11 (1%)	2 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)
Fever (>= 38C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	YES	0	4 (<1%)	11 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
	NO	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
OTHER									
Stayed Home	N	0	1609	1610	1610	1610	1608	1610	1609
	YES	0	7 (<1%)	25 (2%)	6 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)
	NO	0	1602 (100%)	1585 (98%)	1604 (100%)	1606 (100%)	1605 (100%)	1606 (100%)	1606 (100%)
Analgesic Antipyretics	N	1625	1610	1612	1611	1612	1610	1611	1610
	YES	4 (<1%)	75 (5%)	113 (7%)	29 (2%)	24 (1%)	18 (1%)	17 (1%)	13 (1%)
	NO	1621 (100%)	1535 (95%)	1499 (93%)	1582 (98%)	1588 (99%)	1592 (99%)	1594 (99%)	1597 (99%)
Temperature (C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	<38 C	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)
	38 - 38.9 C	0	3 (<1%)	9 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	1 (<1%)	2 (<1%)	0	0	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
		Number (%) of Subjects							
INJECTION SITE									
Pain	N	541	508	509	509	509	509	509	509
	ANY	115 (21%)	60 (12%)	44 (9%)	15 (3%)	8 (2%)	3 (1%)	0	0
	MILD	94 (17%)	41 (8%)	34 (7%)	12 (2%)	8 (2%)	3 (1%)	0	0
	MODERATE	20 (4%)	18 (4%)	9 (2%)	3 (1%)	0	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	541	508	509	509	509	509	509	509
	ANY	46 (9%)	4 (1%)	1 (<1%)	10 (2%)	4 (1%)	0	1 (<1%)	0
	>0 - 25 mm	46 (9%)	4 (1%)	1 (<1%)	6 (1%)	3 (1%)	0	1 (<1%)	0
	>25 - 50 mm	0	0	0	3 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	0	0	1 (<1%)	0	0	0	0
Induration (mm)	N	541	508	509	509	509	509	509	509
	ANY	19 (4%)	12 (2%)	14 (3%)	19 (4%)	6 (1%)	0	0	0
	>0 - 25 mm	19 (4%)	9 (2%)	12 (2%)	12 (2%)	5 (1%)	0	0	0
	>25 - 50 mm	0	1 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	2 (<1%)	1 (<1%)	3 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	541	509	509	509	509	509	509	509
	ANY	10 (2%)	12 (2%)	22 (4%)	8 (2%)	4 (1%)	3 (1%)	4 (1%)	3 (1%)
	MILD	7 (1%)	7 (1%)	17 (3%)	6 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)
	MODERATE	2 (<1%)	5 (1%)	3 (1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0	0
Nausea	N	541	509	509	509	509	509	509	509
	ANY	7 (1%)	16 (3%)	28 (6%)	6 (1%)	6 (1%)	2 (<1%)	5 (1%)	2 (<1%)
	MILD	6 (1%)	10 (2%)	20 (4%)	4 (1%)	3 (1%)	2 (<1%)	4 (1%)	1 (<1%)
	MODERATE	1 (<1%)	5 (1%)	7 (1%)	2 (<1%)	3 (1%)	0	1 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	1 (<1%)	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
SYSTEMIC									
Malaise	N	541	509	509	509	509	509	509	509
	ANY	8 (1%)	34 (7%)	38 (7%)	19 (4%)	3 (1%)	3 (1%)	1 (<1%)	4 (1%)
	MILD	5 (1%)	29 (6%)	30 (6%)	15 (3%)	1 (<1%)	3 (1%)	1 (<1%)	2 (<1%)
	MODERATE	3 (1%)	3 (1%)	7 (1%)	3 (1%)	2 (<1%)	0	0	2 (<1%)
	SEVERE	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
Myalgia	N	541	509	509	509	509	509	509	509
	ANY	24 (4%)	23 (5%)	37 (7%)	11 (2%)	3 (1%)	1 (<1%)	3 (1%)	2 (<1%)
	MILD	17 (3%)	16 (3%)	27 (5%)	7 (1%)	2 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
	MODERATE	7 (1%)	6 (1%)	7 (1%)	3 (1%)	1 (<1%)	0	0	1 (<1%)
	SEVERE	0	1 (<1%)	3 (1%)	1 (<1%)	0	0	0	0
Arthralgia	N	541	509	509	509	509	509	509	509
	ANY	12 (2%)	8 (2%)	23 (5%)	8 (2%)	4 (1%)	3 (1%)	1 (<1%)	3 (1%)
	MILD	10 (2%)	6 (1%)	16 (3%)	7 (1%)	4 (1%)	3 (1%)	0	1 (<1%)
	MODERATE	2 (<1%)	2 (<1%)	6 (1%)	0	0	0	1 (<1%)	1 (<1%)
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Headache	N	541	508	509	509	509	509	509	509
	ANY	42 (8%)	67 (13%)	46 (9%)	17 (3%)	11 (2%)	3 (1%)	5 (1%)	3 (1%)
	MILD	29 (5%)	50 (10%)	32 (6%)	9 (2%)	9 (2%)	1 (<1%)	2 (<1%)	2 (<1%)
	MODERATE	10 (2%)	12 (2%)	11 (2%)	6 (1%)	2 (<1%)	2 (<1%)	3 (1%)	1 (<1%)
	SEVERE	3 (1%)	5 (1%)	3 (1%)	2 (<1%)	0	0	0	0
Rash	N	540	509	509	509	507	508	509	509
	ANY	0	4 (1%)	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	1 (<1%)	0
	OTHER	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	URTICARIAL	0	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)	0
Fever (>= 38C)	N	541	498	504	504	505	504	502	494
	YES	3 (1%)	2 (<1%)	8 (2%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	NO	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
OTHER									
Stayed Home	N	0	509	509	509	509	508	509	509
	YES	0	21 (4%)	13 (3%)	4 (1%)	2 (<1%)	0	0	0
	NO	0	488 (96%)	496 (97%)	505 (99%)	507 (100%)	508 (100%)	509 (100%)	509 (100%)
Analgesic Antipyretics	N	541	508	508	508	508	508	508	508
	YES	0	14 (3%)	31 (6%)	11 (2%)	7 (1%)	2 (<1%)	4 (1%)	4 (1%)
	NO	541 (100%)	494 (97%)	477 (94%)	497 (98%)	501 (99%)	506 (100%)	504 (99%)	504 (99%)
Temperature (C)	N	541	498	504	504	505	504	502	494
	<38 C	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)
	38 - 38.9 C	3 (1%)	2 (<1%)	7 (1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=540)	6HR (N=540)	DAY 2 (N=540)	DAY 3 (N=540)	DAY 4 (N=540)	DAY 5 (N=540)	DAY 6 (N=540)	DAY 7 (N=540)
INJECTION SITE									
Pain	N	540	513	512	513	512	513	513	513
	ANY	109 (20%)	81 (16%)	48 (9%)	19 (4%)	4 (1%)	0	2 (<1%)	0
	MILD	85 (16%)	58 (11%)	41 (8%)	17 (3%)	3 (1%)	0	1 (<1%)	0
	MODERATE	18 (3%)	23 (4%)	6 (1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0
	SEVERE	6 (1%)	0	1 (<1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	540	513	513	513	513	513	513	512
	ANY	37 (7%)	10 (2%)	10 (2%)	8 (2%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	>0 - 25 mm	37 (7%)	10 (2%)	9 (2%)	4 (1%)	0	1 (<1%)	1 (<1%)	0
	>25 - 50 mm	0	0	1 (<1%)	3 (1%)	0	0	0	0
	> 50 mm	0	0	0	1 (<1%)	1 (<1%)	0	0	0
Induration (mm)	N	540	512	512	513	513	513	513	512
	ANY	17 (3%)	14 (3%)	26 (5%)	6 (1%)	4 (1%)	1 (<1%)	0	0
	>0 - 25 mm	16 (3%)	13 (3%)	19 (4%)	3 (1%)	3 (1%)	1 (<1%)	0	0
	>25 - 50 mm	0	1 (<1%)	4 (1%)	1 (<1%)	0	0	0	0
	> 50 mm	1 (<1%)	0	3 (1%)	2 (<1%)	1 (<1%)	0	0	0
SYSTEMIC									
Chills	N	540	513	513	513	513	513	513	513
	ANY	7 (1%)	15 (3%)	30 (6%)	12 (2%)	6 (1%)	2 (<1%)	4 (1%)	1 (<1%)
	MILD	6 (1%)	8 (2%)	16 (3%)	10 (2%)	4 (1%)	1 (<1%)	3 (1%)	1 (<1%)
	MODERATE	1 (<1%)	6 (1%)	10 (2%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	1 (<1%)	4 (1%)	1 (<1%)	0	0	0	0
Nausea	N	540	513	513	513	513	513	513	513
	ANY	14 (3%)	27 (5%)	25 (5%)	6 (1%)	6 (1%)	7 (1%)	2 (<1%)	1 (<1%)
	MILD	12 (2%)	23 (4%)	18 (4%)	5 (1%)	5 (1%)	5 (1%)	2 (<1%)	1 (<1%)
	MODERATE	1 (<1%)	4 (1%)	4 (1%)	0	1 (<1%)	2 (<1%)	0	0
	SEVERE	1 (<1%)	0	3 (1%)	1 (<1%)	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects 30M (N=540)	6HR (N=540)	DAY 2 (N=540)	DAY 3 (N=540)	DAY 4 (N=540)	DAY 5 (N=540)	DAY 6 (N=540)	DAY 7 (N=540)
SYSTEMIC									
Malaise	N	540	513	513	513	513	513	513	513
	ANY	23 (4%)	36 (7%)	46 (9%)	17 (3%)	2 (<1%)	5 (1%)	2 (<1%)	1 (<1%)
	MILD	21 (4%)	22 (4%)	31 (6%)	13 (3%)	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
	MODERATE	2 (<1%)	10 (2%)	13 (3%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	SEVERE	0	4 (1%)	2 (<1%)	2 (<1%)	0	1 (<1%)	0	0
Myalgia	N	540	513	513	513	513	513	513	513
	ANY	42 (8%)	40 (8%)	41 (8%)	15 (3%)	4 (1%)	1 (<1%)	2 (<1%)	0
	MILD	33 (6%)	29 (6%)	29 (6%)	14 (3%)	3 (1%)	1 (<1%)	2 (<1%)	0
	MODERATE	6 (1%)	8 (2%)	7 (1%)	0	1 (<1%)	0	0	0
	SEVERE	3 (1%)	3 (1%)	5 (1%)	1 (<1%)	0	0	0	0
Arthralgia	N	540	513	513	513	513	513	513	513
	ANY	14 (3%)	29 (6%)	33 (6%)	11 (2%)	1 (<1%)	1 (<1%)	5 (1%)	0
	MILD	11 (2%)	21 (4%)	24 (5%)	8 (2%)	1 (<1%)	0	4 (1%)	0
	MODERATE	2 (<1%)	8 (2%)	6 (1%)	2 (<1%)	0	1 (<1%)	1 (<1%)	0
	SEVERE	1 (<1%)	0	3 (1%)	1 (<1%)	0	0	0	0
Headache	N	540	513	513	513	513	513	512	513
	ANY	54 (10%)	50 (10%)	71 (14%)	19 (4%)	12 (2%)	8 (2%)	0	2 (<1%)
	MILD	40 (7%)	41 (8%)	46 (9%)	16 (3%)	9 (2%)	7 (1%)	0	1 (<1%)
	MODERATE	9 (2%)	8 (2%)	15 (3%)	1 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
	SEVERE	5 (1%)	1 (<1%)	10 (2%)	2 (<1%)	1 (<1%)	0	0	0
Rash	N	540	513	513	513	513	513	512	512
	ANY	1 (<1%)	4 (1%)	2 (<1%)	7 (1%)	4 (1%)	0	3 (1%)	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	1 (<1%)	4 (1%)	2 (<1%)	7 (1%)	4 (1%)	0	3 (1%)	0
Fever (>= 38C)	N	540	499	499	499	489	490	488	471
	YES	3 (1%)	4 (1%)	9 (2%)	5 (1%)	3 (1%)	3 (1%)	0	1 (<1%)
	NO	537 (99%)	495 (99%)	490 (98%)	494 (99%)	486 (99%)	487 (99%)	488 (100%)	470 (100%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 28

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY+Concomitant Vaccines by Study
Ages 11-18

Reaction		Number (%) of Subjects							
		30M (N=540)	6HR (N=540)	DAY 2 (N=540)	DAY 3 (N=540)	DAY 4 (N=540)	DAY 5 (N=540)	DAY 6 (N=540)	DAY 7 (N=540)
OTHER									
Stayed Home	N	0	513	513	513	513	513	513	512
	YES	0	31 (6%)	17 (3%)	3 (1%)	3 (1%)	0	0	0
	NO	0	482 (94%)	496 (97%)	510 (99%)	510 (99%)	513 (100%)	513 (100%)	512 (100%)
Analgesic Antipyretics	N	540	513	513	513	513	513	513	513
	YES	4 (1%)	24 (5%)	43 (8%)	15 (3%)	6 (1%)	3 (1%)	4 (1%)	3 (1%)
	NO	536 (99%)	489 (95%)	470 (92%)	498 (97%)	507 (99%)	510 (99%)	509 (99%)	510 (99%)
Temperature (C)	N	540	499	499	499	489	490	488	471
	<38 C	537 (99%)	495 (99%)	490 (98%)	494 (99%)	486 (99%)	487 (99%)	488 (100%)	470 (100%)
	38 - 38.9 C	3 (1%)	4 (1%)	9 (2%)	4 (1%)	3 (1%)	2 (<1%)	0	1 (<1%)
	39.0 - 39.9 C	0	0	0	1 (<1%)	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_CONVAC_11_18.SAS(WARTERO) 10JUL08, 08:34 SAS.9.1 - PINJONSET_MEN_VS_CONVAC_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P6 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
INJECTION SITE									
Pain	N	151	150	150	150	149	150	149	149
	ANY	26 (17%)	31 (21%)	21 (14%)	3 (2%)	0	0	0	0
	MILD	23 (15%)	29 (19%)	19 (13%)	3 (2%)	0	0	0	0
	MODERATE	3 (2%)	2 (1%)	2 (1%)	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Erythema (mm)	N	151	148	148	148	147	148	148	147
	ANY	48 (32%)	2 (1%)	5 (3%)	2 (1%)	0	0	0	0
	>0 - 25 mm	45 (30%)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0
	>25 - 50 mm	3 (2%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	1 (1%)	3 (2%)	1 (1%)	0	0	0	0
Induration (mm)	N	151	149	149	149	148	149	149	148
	ANY	22 (15%)	3 (2%)	8 (5%)	1 (1%)	0	0	0	0
	>0 - 25 mm	20 (13%)	3 (2%)	4 (3%)	0	0	0	0	0
	>25 - 50 mm	2 (1%)	0	1 (1%)	0	0	0	0	0
	> 50 mm	0	0	3 (2%)	1 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	12 (8%)	1 (1%)	5 (3%)	0	1 (1%)	2 (1%)
	MILD	0	2 (1%)	8 (5%)	1 (1%)	4 (3%)	0	1 (1%)	1 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	2 (1%)	0	0	0	0	0
Nausea	N	151	150	150	150	149	150	150	149
	ANY	2 (1%)	5 (3%)	8 (5%)	1 (1%)	2 (1%)	0	0	4 (3%)
	MILD	2 (1%)	4 (3%)	6 (4%)	0	1 (1%)	0	0	2 (1%)
	MODERATE	0	1 (1%)	2 (1%)	0	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	0	1 (1%)	0	0	0	1 (1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
SYSTEMIC									
Malaise	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	0	13 (9%)	1 (1%)	2 (1%)	0	4 (3%)	2 (1%)
	MILD	1 (1%)	0	9 (6%)	0	1 (1%)	0	2 (1%)	1 (1%)
	MODERATE	0	0	2 (1%)	0	1 (1%)	0	2 (1%)	1 (1%)
	SEVERE	0	0	2 (1%)	1 (1%)	0	0	0	0
Myalgia	N	151	150	150	150	149	150	150	149
	ANY	1 (1%)	14 (9%)	7 (5%)	8 (5%)	3 (2%)	1 (1%)	1 (1%)	0
	MILD	1 (1%)	12 (8%)	3 (2%)	8 (5%)	2 (1%)	1 (1%)	1 (1%)	0
	MODERATE	0	2 (1%)	3 (2%)	0	1 (1%)	0	0	0
	SEVERE	0	0	1 (1%)	0	0	0	0	0
Arthralgia	N	151	150	150	150	149	150	150	149
	ANY	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MILD	0	3 (2%)	1 (1%)	3 (2%)	0	2 (1%)	2 (1%)	1 (1%)
	MODERATE	0	0	0	0	0	0	0	0
	SEVERE	0	0	0	0	0	0	0	0
Headache	N	151	150	150	150	149	150	150	149
	ANY	11 (7%)	9 (6%)	24 (16%)	3 (2%)	3 (2%)	3 (2%)	6 (4%)	3 (2%)
	MILD	11 (7%)	9 (6%)	16 (11%)	1 (1%)	2 (1%)	3 (2%)	5 (3%)	2 (1%)
	MODERATE	0	0	5 (3%)	1 (1%)	1 (1%)	0	0	1 (1%)
	SEVERE	0	0	3 (2%)	1 (1%)	0	0	1 (1%)	0
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P6 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=151)	6HR (N=151)	DAY 2 (N=151)	DAY 3 (N=151)	DAY 4 (N=151)	DAY 5 (N=151)	DAY 6 (N=151)	DAY 7 (N=151)
SYSTEMIC									
Fever (>= 38C)	N	151	149	149	146	144	146	147	148
	YES	0	0	0	0	0	0	0	1 (1%)
	NO	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)
OTHER									
Stayed Home	N	0	150	149	149	148	149	148	148
	YES	0	0	4 (3%)	1 (1%)	0	0	1 (1%)	0
	NO	0	150 (100%)	145 (97%)	148 (99%)	148 (100%)	149 (100%)	147 (99%)	148 (100%)
Analgesic Antipyretics	N	151	150	149	149	148	149	148	148
	YES	2 (1%)	7 (5%)	15 (10%)	3 (2%)	4 (3%)	2 (1%)	3 (2%)	3 (2%)
	NO	149 (99%)	143 (95%)	134 (90%)	146 (98%)	144 (97%)	147 (99%)	145 (98%)	145 (98%)
Temperature (C)	N	151	149	149	146	144	146	147	148
	<38 C	151 (100%)	149 (100%)	149 (100%)	146 (100%)	144 (100%)	146 (100%)	147 (100%)	147 (99%)
	38 - 38.9 C	0	0	0	0	0	0	0	1 (1%)
	39.0 - 39.9 C	0	0	0	0	0	0	0	0
	>= 40 C	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P11 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
INJECTION SITE									
Pain	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	67 (19%)	28 (8%)	10 (3%)	1 (<1%)	1 (<1%)	0	0
	MILD	6 (2%)	51 (14%)	24 (7%)	8 (2%)	0	1 (<1%)	0	0
	MODERATE	3 (1%)	12 (3%)	3 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	0	4 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Erythema (mm)	N	357	357	357	357	357	357	357	357
	ANY	9 (3%)	40 (11%)	11 (3%)	6 (2%)	0	0	0	0
	>0 - 25 mm	9 (3%)	40 (11%)	9 (3%)	3 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	0
	> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	N	357	357	357	357	357	357	357	357
	ANY	5 (1%)	29 (8%)	17 (5%)	7 (2%)	0	0	0	1 (<1%)
	>0 - 25 mm	5 (1%)	28 (8%)	15 (4%)	4 (1%)	0	0	0	0
	>25 - 50 mm	0	0	2 (1%)	3 (1%)	0	0	0	1 (<1%)
	> 50 mm	0	1 (<1%)	0	0	0	0	0	0
SYSTEMIC									
Chills	N	357	357	357	357	357	357	357	357
	ANY	0	21 (6%)	7 (2%)	6 (2%)	3 (1%)	5 (1%)	2 (1%)	3 (1%)
	MILD	0	14 (4%)	5 (1%)	3 (1%)	0	3 (1%)	2 (1%)	3 (1%)
	MODERATE	0	5 (1%)	2 (1%)	2 (1%)	2 (1%)	2 (1%)	0	0
	SEVERE	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0	0
Nausea	N	357	357	357	357	357	357	357	357
	ANY	0	8 (2%)	9 (3%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	3 (1%)
	MILD	0	6 (2%)	7 (2%)	2 (1%)	1 (<1%)	0	2 (1%)	3 (1%)
	MODERATE	0	2 (1%)	2 (1%)	1 (<1%)	0	0	0	0
	SEVERE	0	0	0	0	0	2 (1%)	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P11 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
SYSTEMIC									
Malaise	N	357	357	357	357	357	357	357	357
	ANY	0	24 (7%)	7 (2%)	6 (2%)	2 (1%)	2 (1%)	0	2 (1%)
	MILD	0	17 (5%)	3 (1%)	4 (1%)	2 (1%)	1 (<1%)	0	1 (<1%)
	MODERATE	0	7 (2%)	4 (1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)
	SEVERE	0	0	0	1 (<1%)	0	0	0	0
Myalgia	N	357	357	357	357	357	357	357	357
	ANY	0	46 (13%)	18 (5%)	10 (3%)	2 (1%)	2 (1%)	1 (<1%)	0
	MILD	0	33 (9%)	12 (3%)	7 (2%)	2 (1%)	2 (1%)	0	0
	MODERATE	0	10 (3%)	6 (2%)	2 (1%)	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	0	1 (<1%)	0	0	0	0
Arthralgia	N	357	357	357	357	357	357	357	357
	ANY	0	23 (6%)	8 (2%)	3 (1%)	1 (<1%)	1 (<1%)	2 (1%)	2 (1%)
	MILD	0	15 (4%)	5 (1%)	2 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
	MODERATE	0	5 (1%)	2 (1%)	0	0	0	1 (<1%)	0
	SEVERE	0	3 (1%)	1 (<1%)	1 (<1%)	0	0	0	0
Headache	N	357	357	357	357	357	357	357	357
	ANY	3 (1%)	64 (18%)	29 (8%)	10 (3%)	6 (2%)	9 (3%)	4 (1%)	3 (1%)
	MILD	3 (1%)	45 (13%)	21 (6%)	9 (3%)	5 (1%)	6 (2%)	3 (1%)	2 (1%)
	MODERATE	0	13 (4%)	5 (1%)	1 (<1%)	0	3 (1%)	0	0
	SEVERE	0	6 (2%)	3 (1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Rash	N	0	0	0	0	0	0	0	0
	ANY	0	0	0	0	0	0	0	0
	OTHER	0	0	0	0	0	0	0	0
	URTICARIAL	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P11 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=357)	6HR (N=357)	DAY 2 (N=357)	DAY 3 (N=357)	DAY 4 (N=357)	DAY 5 (N=357)	DAY 6 (N=357)	DAY 7 (N=357)
SYSTEMIC									
Fever (>= 38C)	N	357	356	356	357	356	355	355	353
	YES	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	3 (1%)	2 (1%)	0
	NO	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)
OTHER									
Stayed Home	N	0	357	357	357	357	357	357	356
	YES	0	1 (<1%)	4 (1%)	3 (1%)	2 (1%)	2 (1%)	0	0
	NO	0	356 (100%)	353 (99%)	354 (99%)	355 (99%)	355 (99%)	357 (100%)	356 (100%)
Analgesic Antipyretics	N	357	357	357	357	357	357	357	356
	YES	0	6 (2%)	8 (2%)	5 (1%)	4 (1%)	3 (1%)	2 (1%)	3 (1%)
	NO	357 (100%)	351 (98%)	349 (98%)	352 (99%)	353 (99%)	354 (99%)	355 (99%)	353 (99%)
Temperature (C)	N	357	356	356	357	356	355	355	353
	<38 C	357 (100%)	354 (99%)	353 (99%)	354 (99%)	355 (100%)	352 (99%)	353 (99%)	353 (100%)
	38 - 38.9 C	0	2 (1%)	3 (1%)	3 (1%)	1 (<1%)	2 (1%)	2 (1%)	0
	39.0 - 39.9 C	0	0	0	0	0	1 (<1%)	0	0
	>= 40 C	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P13 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
INJECTION SITE									
Pain	N	1622	1607	1610	1610	1609	1607	1609	1607
	ANY	212 (13%)	296 (18%)	145 (9%)	44 (3%)	9 (1%)	7 (<1%)	0	1 (<1%)
	MILD	197 (12%)	260 (16%)	120 (7%)	43 (3%)	6 (<1%)	7 (<1%)	0	1 (<1%)
	MODERATE	14 (1%)	35 (2%)	22 (1%)	1 (<1%)	2 (<1%)	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	3 (<1%)	0	1 (<1%)	0	0	0
Erythema (mm)	N	1623	1607	1611	1611	1610	1610	1609	1608
	ANY	64 (4%)	57 (4%)	80 (5%)	34 (2%)	6 (<1%)	4 (<1%)	2 (<1%)	0
	>0 - 25 mm	61 (4%)	53 (3%)	56 (3%)	20 (1%)	4 (<1%)	3 (<1%)	2 (<1%)	0
	>25 - 50 mm	3 (<1%)	1 (<1%)	13 (1%)	9 (1%)	2 (<1%)	1 (<1%)	0	0
	> 50 mm	0	3 (<1%)	11 (1%)	5 (<1%)	0	0	0	0
Induration (mm)	N	1623	1607	1611	1610	1610	1610	1609	1608
	ANY	34 (2%)	55 (3%)	76 (5%)	26 (2%)	1 (<1%)	2 (<1%)	2 (<1%)	0
	>0 - 25 mm	34 (2%)	45 (3%)	53 (3%)	12 (1%)	0	2 (<1%)	2 (<1%)	0
	>25 - 50 mm	0	7 (<1%)	13 (1%)	9 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	3 (<1%)	10 (1%)	5 (<1%)	0	0	0	0
SYSTEMIC									
Chills	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	18 (1%)	27 (2%)	49 (3%)	13 (1%)	6 (<1%)	9 (1%)	1 (<1%)	4 (<1%)
	MILD	16 (1%)	24 (1%)	31 (2%)	10 (1%)	6 (<1%)	4 (<1%)	1 (<1%)	0
	MODERATE	2 (<1%)	1 (<1%)	15 (1%)	3 (<1%)	0	5 (<1%)	0	3 (<1%)
	SEVERE	0	2 (<1%)	3 (<1%)	0	0	0	0	1 (<1%)
Nausea	N	1625	1610	1613	1613	1612	1612	1612	1610
	ANY	14 (1%)	41 (3%)	62 (4%)	26 (2%)	16 (1%)	11 (1%)	9 (1%)	8 (<1%)
	MILD	12 (1%)	36 (2%)	42 (3%)	16 (1%)	12 (1%)	7 (<1%)	6 (<1%)	4 (<1%)
	MODERATE	2 (<1%)	5 (<1%)	17 (1%)	7 (<1%)	4 (<1%)	4 (<1%)	1 (<1%)	4 (<1%)
	SEVERE	0	0	3 (<1%)	3 (<1%)	0	0	2 (<1%)	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P13 ACWY

Reaction[1]		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	17 (1%)	33 (2%)	71 (4%)	26 (2%)	8 (<1%)	7 (<1%)	9 (1%)	6 (<1%)
	MILD	15 (1%)	25 (2%)	39 (2%)	16 (1%)	7 (<1%)	4 (<1%)	6 (<1%)	3 (<1%)
	MODERATE	2 (<1%)	8 (<1%)	23 (1%)	9 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	0	0	9 (1%)	1 (<1%)	0	1 (<1%)	0	0
Myalgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	31 (2%)	112 (7%)	102 (6%)	31 (2%)	6 (<1%)	15 (1%)	6 (<1%)	7 (<1%)
	MILD	28 (2%)	95 (6%)	74 (5%)	24 (1%)	6 (<1%)	14 (1%)	2 (<1%)	4 (<1%)
	MODERATE	1 (<1%)	14 (1%)	20 (1%)	7 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)
	SEVERE	2 (<1%)	3 (<1%)	8 (<1%)	0	0	0	1 (<1%)	0
Arthralgia	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	9 (1%)	25 (2%)	53 (3%)	20 (1%)	7 (<1%)	13 (1%)	4 (<1%)	6 (<1%)
	MILD	9 (1%)	22 (1%)	41 (3%)	19 (1%)	5 (<1%)	9 (1%)	2 (<1%)	5 (<1%)
	MODERATE	0	2 (<1%)	8 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	4 (<1%)	0	0	1 (<1%)	0	0
Headache	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	63 (4%)	131 (8%)	134 (8%)	44 (3%)	41 (3%)	27 (2%)	26 (2%)	12 (1%)
	MILD	57 (4%)	102 (6%)	99 (6%)	31 (2%)	33 (2%)	21 (1%)	20 (1%)	8 (<1%)
	MODERATE	5 (<1%)	25 (2%)	29 (2%)	12 (1%)	7 (<1%)	5 (<1%)	3 (<1%)	4 (<1%)
	SEVERE	1 (<1%)	4 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
Rash	N	1625	1609	1612	1612	1611	1611	1611	1609
	ANY	0	4 (<1%)	15 (1%)	9 (1%)	4 (<1%)	6 (<1%)	3 (<1%)	3 (<1%)
	OTHER	0	3 (<1%)	4 (<1%)	7 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
	URTICARIAL	0	1 (<1%)	11 (1%)	2 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P13 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=1631)	6HR (N=1631)	DAY 2 (N=1631)	DAY 3 (N=1631)	DAY 4 (N=1631)	DAY 5 (N=1631)	DAY 6 (N=1631)	DAY 7 (N=1631)
SYSTEMIC									
Fever (>= 38C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	YES	0	4 (<1%)	11 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
	NO	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)
OTHER									
Stayed Home	N	0	1609	1610	1610	1610	1608	1610	1609
	YES	0	7 (<1%)	25 (2%)	6 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)
	NO	0	1602 (100%)	1585 (98%)	1604 (100%)	1606 (100%)	1605 (100%)	1606 (100%)	1606 (100%)
Analgesic Antipyretics	N	1625	1610	1612	1611	1612	1610	1611	1610
	YES	4 (<1%)	75 (5%)	113 (7%)	29 (2%)	24 (1%)	18 (1%)	17 (1%)	13 (1%)
	NO	1621 (100%)	1535 (95%)	1499 (93%)	1582 (98%)	1588 (99%)	1592 (99%)	1594 (99%)	1597 (99%)
Temperature (C)	N	1615	1581	1586	1587	1580	1581	1579	1571
	<38 C	1615 (100%)	1577 (100%)	1575 (99%)	1584 (100%)	1578 (100%)	1580 (100%)	1578 (100%)	1570 (100%)
	38 - 38.9 C	0	3 (<1%)	9 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	1 (<1%)	2 (<1%)	0	0	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P18 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
INJECTION SITE									
Pain	N	541	508	509	509	509	509	509	509
	ANY	115 (21%)	60 (12%)	44 (9%)	15 (3%)	8 (2%)	3 (1%)	0	0
	MILD	94 (17%)	41 (8%)	34 (7%)	12 (2%)	8 (2%)	3 (1%)	0	0
	MODERATE	20 (4%)	18 (4%)	9 (2%)	3 (1%)	0	0	0	0
	SEVERE	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0
Erythema (mm)	N	541	508	509	509	509	509	509	509
	ANY	46 (9%)	4 (1%)	1 (<1%)	10 (2%)	4 (1%)	0	1 (<1%)	0
	>0 - 25 mm	46 (9%)	4 (1%)	1 (<1%)	6 (1%)	3 (1%)	0	1 (<1%)	0
	>25 - 50 mm	0	0	0	3 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	0	0	1 (<1%)	0	0	0	0
Induration (mm)	N	541	508	509	509	509	509	509	509
	ANY	19 (4%)	12 (2%)	14 (3%)	19 (4%)	6 (1%)	0	0	0
	>0 - 25 mm	19 (4%)	9 (2%)	12 (2%)	12 (2%)	5 (1%)	0	0	0
	>25 - 50 mm	0	1 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	0	0	0
	> 50 mm	0	2 (<1%)	1 (<1%)	3 (1%)	0	0	0	0
SYSTEMIC									
Chills	N	541	509	509	509	509	509	509	509
	ANY	10 (2%)	12 (2%)	22 (4%)	8 (2%)	4 (1%)	3 (1%)	4 (1%)	3 (1%)
	MILD	7 (1%)	7 (1%)	17 (3%)	6 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)
	MODERATE	2 (<1%)	5 (1%)	3 (1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
	SEVERE	1 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0	0
Nausea	N	541	509	509	509	509	509	509	509
	ANY	7 (1%)	16 (3%)	28 (6%)	6 (1%)	6 (1%)	2 (<1%)	5 (1%)	2 (<1%)
	MILD	6 (1%)	10 (2%)	20 (4%)	4 (1%)	3 (1%)	2 (<1%)	4 (1%)	1 (<1%)
	MODERATE	1 (<1%)	5 (1%)	7 (1%)	2 (<1%)	3 (1%)	0	1 (<1%)	1 (<1%)
	SEVERE	0	1 (<1%)	1 (<1%)	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P18 ACWY

Reaction[1]		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
		Number (%) of Subjects							
SYSTEMIC									
Malaise	N	541	509	509	509	509	509	509	509
	ANY	8 (1%)	34 (7%)	38 (7%)	19 (4%)	3 (1%)	3 (1%)	1 (<1%)	4 (1%)
	MILD	5 (1%)	29 (6%)	30 (6%)	15 (3%)	1 (<1%)	3 (1%)	1 (<1%)	2 (<1%)
	MODERATE	3 (1%)	3 (1%)	7 (1%)	3 (1%)	2 (<1%)	0	0	2 (<1%)
	SEVERE	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
Myalgia	N	541	509	509	509	509	509	509	509
	ANY	24 (4%)	23 (5%)	37 (7%)	11 (2%)	3 (1%)	1 (<1%)	3 (1%)	2 (<1%)
	MILD	17 (3%)	16 (3%)	27 (5%)	7 (1%)	2 (<1%)	1 (<1%)	3 (1%)	1 (<1%)
	MODERATE	7 (1%)	6 (1%)	7 (1%)	3 (1%)	1 (<1%)	0	0	1 (<1%)
	SEVERE	0	1 (<1%)	3 (1%)	1 (<1%)	0	0	0	0
Arthralgia	N	541	509	509	509	509	509	509	509
	ANY	12 (2%)	8 (2%)	23 (5%)	8 (2%)	4 (1%)	3 (1%)	1 (<1%)	3 (1%)
	MILD	10 (2%)	6 (1%)	16 (3%)	7 (1%)	4 (1%)	3 (1%)	0	1 (<1%)
	MODERATE	2 (<1%)	2 (<1%)	6 (1%)	0	0	0	1 (<1%)	1 (<1%)
	SEVERE	0	0	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)
Headache	N	541	508	509	509	509	509	509	509
	ANY	42 (8%)	67 (13%)	46 (9%)	17 (3%)	11 (2%)	3 (1%)	5 (1%)	3 (1%)
	MILD	29 (5%)	50 (10%)	32 (6%)	9 (2%)	9 (2%)	1 (<1%)	2 (<1%)	2 (<1%)
	MODERATE	10 (2%)	12 (2%)	11 (2%)	6 (1%)	2 (<1%)	2 (<1%)	3 (1%)	1 (<1%)
	SEVERE	3 (1%)	5 (1%)	3 (1%)	2 (<1%)	0	0	0	0
Rash	N	540	509	509	509	507	508	509	509
	ANY	0	4 (1%)	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	1 (<1%)	0
	OTHER	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	URTICARIAL	0	4 (1%)	3 (1%)	3 (1%)	2 (<1%)	2 (<1%)	1 (<1%)	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Group: P18 ACWY

Reaction[1]		Number (%) of Subjects							
		30M (N=541)	6HR (N=541)	DAY 2 (N=541)	DAY 3 (N=541)	DAY 4 (N=541)	DAY 5 (N=541)	DAY 6 (N=541)	DAY 7 (N=541)
SYSTEMIC									
Fever (>= 38C)	N	541	498	504	504	505	504	502	494
	YES	3 (1%)	2 (<1%)	8 (2%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	NO	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)
OTHER									
Stayed Home	N	0	509	509	509	509	508	509	509
	YES	0	21 (4%)	13 (3%)	4 (1%)	2 (<1%)	0	0	0
	NO	0	488 (96%)	496 (97%)	505 (99%)	507 (100%)	508 (100%)	509 (100%)	509 (100%)
Analgesic Antipyretics	N	541	508	508	508	508	508	508	508
	YES	0	14 (3%)	31 (6%)	11 (2%)	7 (1%)	2 (<1%)	4 (1%)	4 (1%)
	NO	541 (100%)	494 (97%)	477 (94%)	497 (98%)	501 (99%)	506 (100%)	504 (99%)	504 (99%)
Temperature (C)	N	541	498	504	504	505	504	502	494
	<38 C	538 (99%)	496 (100%)	496 (98%)	503 (100%)	504 (100%)	502 (100%)	501 (100%)	493 (100%)
	38 - 38.9 C	3 (1%)	2 (<1%)	7 (1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0
	39.0 - 39.9 C	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		30M (N=503)	6HR (N=503)	DAY 2 (N=503)	DAY 3 (N=503)	DAY 4 (N=503)	DAY 5 (N=503)	DAY 6 (N=503)	DAY 7 (N=503)
		Number (%) of Subjects							
INJECTION SITE									
Pain	N	503	486	486	484	485	484	484	484
	ANY	116 (23%)	81 (17%)	35 (7%)	3 (1%)	2 (<1%)	2 (<1%)	0	0
	MILD	91 (18%)	62 (13%)	26 (5%)	3 (1%)	2 (<1%)	2 (<1%)	0	0
	MODERATE	24 (5%)	16 (3%)	6 (1%)	0	0	0	0	0
	SEVERE	1 (<1%)	3 (1%)	3 (1%)	0	0	0	0	0
Erythema (mm)	N	503	485	485	484	484	484	484	484
	ANY	28 (6%)	15 (3%)	11 (2%)	9 (2%)	1 (<1%)	0	0	0
	>0 - 25 mm	27 (5%)	14 (3%)	8 (2%)	7 (1%)	1 (<1%)	0	0	0
	>25 - 50 mm	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
	> 50 mm	0	0	2 (<1%)	1 (<1%)	0	0	0	0
Induration (mm)	N	503	484	485	485	485	484	484	484
	ANY	16 (3%)	26 (5%)	15 (3%)	5 (1%)	1 (<1%)	1 (<1%)	0	0
	>0 - 25 mm	14 (3%)	20 (4%)	13 (3%)	5 (1%)	1 (<1%)	1 (<1%)	0	0
	>25 - 50 mm	2 (<1%)	4 (1%)	1 (<1%)	0	0	0	0	0
	> 50 mm	0	2 (<1%)	1 (<1%)	0	0	0	0	0
SYSTEMIC									
Chills	N	503	485	486	485	485	484	484	484
	ANY	8 (2%)	10 (2%)	21 (4%)	3 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	MILD	7 (1%)	9 (2%)	14 (3%)	3 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
	MODERATE	0	1 (<1%)	4 (1%)	0	0	0	0	0
	SEVERE	1 (<1%)	0	3 (1%)	0	0	0	0	0
Nausea	N	503	485	486	485	485	484	484	484
	ANY	13 (3%)	8 (2%)	21 (4%)	8 (2%)	4 (1%)	1 (<1%)	5 (1%)	4 (1%)
	MILD	11 (2%)	8 (2%)	15 (3%)	7 (1%)	2 (<1%)	0	4 (1%)	4 (1%)
	MODERATE	1 (<1%)	0	5 (1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
	SEVERE	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects							
		30M (N=503)	6HR (N=503)	DAY 2 (N=503)	DAY 3 (N=503)	DAY 4 (N=503)	DAY 5 (N=503)	DAY 6 (N=503)	DAY 7 (N=503)
SYSTEMIC									
Malaise	N	503	485	486	485	485	484	484	484
	ANY	17 (3%)	22 (5%)	33 (7%)	5 (1%)	2 (<1%)	2 (<1%)	4 (1%)	2 (<1%)
	MILD	14 (3%)	16 (3%)	22 (5%)	4 (1%)	0	2 (<1%)	4 (1%)	1 (<1%)
	MODERATE	1 (<1%)	5 (1%)	6 (1%)	1 (<1%)	2 (<1%)	0	0	0
	SEVERE	2 (<1%)	1 (<1%)	5 (1%)	0	0	0	0	1 (<1%)
Myalgia	N	503	485	486	485	485	484	484	484
	ANY	21 (4%)	26 (5%)	27 (6%)	4 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	0
	MILD	18 (4%)	19 (4%)	20 (4%)	3 (1%)	0	1 (<1%)	1 (<1%)	0
	MODERATE	2 (<1%)	4 (1%)	7 (1%)	1 (<1%)	1 (<1%)	0	0	0
	SEVERE	1 (<1%)	3 (1%)	0	0	0	0	1 (<1%)	0
Arthralgia	N	503	485	486	484	484	484	484	484
	ANY	13 (3%)	11 (2%)	12 (2%)	8 (2%)	3 (1%)	1 (<1%)	2 (<1%)	2 (<1%)
	MILD	10 (2%)	8 (2%)	8 (2%)	7 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	MODERATE	2 (<1%)	3 (1%)	4 (1%)	1 (<1%)	2 (<1%)	0	0	0
	SEVERE	1 (<1%)	0	0	0	0	0	0	0
Headache	N	503	485	486	485	485	484	484	484
	ANY	35 (7%)	36 (7%)	39 (8%)	9 (2%)	10 (2%)	7 (1%)	1 (<1%)	1 (<1%)
	MILD	25 (5%)	28 (6%)	24 (5%)	4 (1%)	8 (2%)	3 (1%)	0	1 (<1%)
	MODERATE	8 (2%)	6 (1%)	12 (2%)	5 (1%)	2 (<1%)	4 (1%)	0	0
	SEVERE	2 (<1%)	2 (<1%)	3 (1%)	0	0	0	1 (<1%)	0
Rash	N	503	486	486	485	485	484	484	484
	ANY	1 (<1%)	7 (1%)	1 (<1%)	3 (1%)	1 (<1%)	0	0	0
	OTHER	1 (<1%)	0	0	1 (<1%)	0	0	0	0
	URTICARIAL	0	7 (1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 29

Summary of Time of First Onset of Reactogenicity, MenACWY alone vs MenACWY after Tdap by Study
Ages 11-18

Reaction[1]		Number (%) of Subjects							
		30M (N=503)	6HR (N=503)	DAY 2 (N=503)	DAY 3 (N=503)	DAY 4 (N=503)	DAY 5 (N=503)	DAY 6 (N=503)	DAY 7 (N=503)
SYSTEMIC									
Fever (>= 38C)	N	503	483	484	483	483	481	479	474
	YES	2 (<1%)	6 (1%)	8 (2%)	3 (1%)	4 (1%)	1 (<1%)	2 (<1%)	4 (1%)
	NO	501 (100%)	477 (99%)	476 (98%)	480 (99%)	479 (99%)	480 (100%)	477 (100%)	470 (99%)
OTHER									
Stayed Home	N	0	485	486	485	485	485	485	485
	YES	0	14 (3%)	8 (2%)	2 (<1%)	0	1 (<1%)	0	0
	NO	0	471 (97%)	478 (98%)	483 (100%)	485 (100%)	484 (100%)	485 (100%)	485 (100%)
Analgesic Antipyretics	N	503	485	486	485	485	484	484	484
	YES	2 (<1%)	10 (2%)	26 (5%)	4 (1%)	5 (1%)	2 (<1%)	1 (<1%)	1 (<1%)
	NO	501 (100%)	475 (98%)	460 (95%)	481 (99%)	480 (99%)	482 (100%)	483 (100%)	483 (100%)
Temperature (C)	N	503	483	484	483	483	481	479	474
	<38 C	501 (100%)	477 (99%)	476 (98%)	480 (99%)	479 (99%)	480 (100%)	477 (100%)	470 (99%)
	38 - 38.9 C	2 (<1%)	5 (1%)	7 (1%)	3 (1%)	3 (1%)	1 (<1%)	2 (<1%)	3 (1%)
	39.0 - 39.9 C	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJONSET_MEN_VS_TDAP_11_18.SAS(WARTERO) 10JUL08, 08:36 SAS.9.1 - PINJONSET_MEN_VS_TDAP_11_18

Table 30

Summary of Treatment-emergent Adverse Events During Month 1 in Descending Frequency, Comparing Total MenACWY[1] across Age Groups
Adverse Events Occurring in at least 1% of Subjects

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
HEADACHE	58 (2%)	29 (3%)	31 (2%)	118 (2%)	37 (2%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUMFRQ_ACWY_M1

Table 31

Summary of Treatment-emergent Adverse Events During Months 2 to 6 in Descending Frequency, Comparing Total MenACWY[1] across Age Groups
Adverse Events Occurring in at least 1% of Subjects
(Study V59P18 excluded)

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUMFRQ_ACWY_M26

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	586 (16%)	205 (18%)	285 (20%)	1076 (17%)	356 (20%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	6 (<1%)	4 (<1%)	9 (1%)	19 (<1%)	3 (<1%)
LYMPH NODE PAIN	0	1 (<1%)	0	1 (<1%)	0
LYMPHADENOPATHY	6 (<1%)	3 (<1%)	9 (1%)	18 (<1%)	3 (<1%)
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	0	1 (<1%)	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	0	1 (<1%)	0
EAR & LABYRINTH DISORDERS	9 (<1%)	3 (<1%)	4 (<1%)	16 (<1%)	9 (1%)
AURICULAR SWELLING	1 (<1%)	0	0	1 (<1%)	0
EAR PAIN	5 (<1%)	1 (<1%)	1 (<1%)	7 (<1%)	4 (<1%)
MOTION SICKNESS	1 (<1%)	0	0	1 (<1%)	1 (<1%)
TINNITUS	0	0	2 (<1%)	2 (<1%)	0
VERTIGO	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	4 (<1%)
ENDOCRINE DISORDERS	1 (<1%)	0	0	1 (<1%)	0
CUSHING'S SYNDROME	1 (<1%)	0	0	1 (<1%)	0
EYE DISORDERS	7 (<1%)	3 (<1%)	5 (<1%)	15 (<1%)	7 (<1%)
BLEPHARITIS	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CONJUNCTIVITIS	3 (<1%)	2 (<1%)	0	5 (<1%)	3 (<1%)
CONJUNCTIVITIS ALLERGIC	0	0	0	0	1 (<1%)
EYE ALLERGY	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
EYE DISORDERS					
EYE DISCHARGE	0	0	1 (<1%)	1 (<1%)	0
EYE IRRITATION	0	1 (<1%)	1 (<1%)	2 (<1%)	0
EYE PAIN	2 (<1%)	0	0	2 (<1%)	1 (<1%)
EYE PRURITUS	0	0	0	0	1 (<1%)
EYE SWELLING	0	0	1 (<1%)	1 (<1%)	0
OCULAR HYPERAEMIA	1 (<1%)	0	0	1 (<1%)	0
TRICHIASIS	0	0	1 (<1%)	1 (<1%)	0
GASTROINTESTINAL DISORDERS	94 (3%)	44 (4%)	38 (3%)	176 (3%)	63 (4%)
ABDOMINAL DISTENSION	0	0	0	0	1 (<1%)
ABDOMINAL PAIN	11 (<1%)	6 (1%)	4 (<1%)	21 (<1%)	12 (1%)
ABDOMINAL PAIN UPPER	16 (<1%)	6 (1%)	2 (<1%)	24 (<1%)	3 (<1%)
APHTHOUS STOMATITIS	1 (<1%)	0	0	1 (<1%)	1 (<1%)
COLITIS	1 (<1%)	0	0	1 (<1%)	1 (<1%)
CONSTIPATION	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
DIARRHOEA	16 (<1%)	12 (1%)	9 (1%)	37 (1%)	17 (1%)
DRY MOUTH	0	0	1 (<1%)	1 (<1%)	1 (<1%)
DYSPEPSIA	0	2 (<1%)	6 (<1%)	8 (<1%)	3 (<1%)
ENTEROCOLITIS	1 (<1%)	0	0	1 (<1%)	0
FOOD POISONING	0	1 (<1%)	1 (<1%)	2 (<1%)	0
GASTRITIS	2 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	2 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
GASTROINTESTINAL DISORDERS					
GASTROINTESTINAL INFLAMMATION	0	0	0	0	1 (<1%)
GASTROINTESTINAL PAIN	0	0	1 (<1%)	1 (<1%)	0
GASTROOESOPHAGEAL REFLUX DISEASE	0	0	1 (<1%)	1 (<1%)	1 (<1%)
GINGIVAL PAIN	1 (<1%)	1 (<1%)	0	2 (<1%)	0
GINGIVITIS	1 (<1%)	0	0	1 (<1%)	0
GLOSSODYNIA	0	0	1 (<1%)	1 (<1%)	0
HAEMORRHOIDS	0	0	2 (<1%)	2 (<1%)	0
HYPERCHLORHYDRIA	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
LIP OEDEMA	0	0	0	0	1 (<1%)
MELAENA	0	0	1 (<1%)	1 (<1%)	0
NAUSEA	25 (1%)	12 (1%)	3 (<1%)	40 (1%)	7 (<1%)
ODYNOPHAGIA	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
ORAL PAIN	1 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
RECTAL HAEMORRHAGE	1 (<1%)	0	0	1 (<1%)	0
STOMACH DISCOMFORT	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
STOMATITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
TOOTHACHE	9 (<1%)	2 (<1%)	0	11 (<1%)	5 (<1%)
VOMITING	18 (1%)	1 (<1%)	5 (<1%)	24 (<1%)	9 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	106 (3%)	47 (4%)	76 (5%)	229 (4%)	50 (3%)
APPLICATION SITE PRURITUS	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
GEN. DISORDERS & ADMIN. SITE COND.					
ASTHENIA	4 (<1%)	0	1 (<1%)	5 (<1%)	2 (<1%)
AXILLARY PAIN	2 (<1%)	1 (<1%)	2 (<1%)	5 (<1%)	0
CHEST DISCOMFORT	2 (<1%)	0	0	2 (<1%)	0
CHEST PAIN	3 (<1%)	3 (<1%)	1 (<1%)	7 (<1%)	2 (<1%)
CHILLS	6 (<1%)	3 (<1%)	6 (<1%)	15 (<1%)	2 (<1%)
DISCOMFORT	0	0	1 (<1%)	1 (<1%)	0
FATIGUE	4 (<1%)	3 (<1%)	6 (<1%)	13 (<1%)	2 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
HUNGER	1 (<1%)	0	0	1 (<1%)	0
INDURATION	4 (<1%)	1 (<1%)	5 (<1%)	10 (<1%)	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	5 (<1%)	5 (<1%)	11 (<1%)	3 (<1%)
INJECTION SITE ANAESTHESIA	0	0	0	0	1 (<1%)
INJECTION SITE BRUISING	4 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
INJECTION SITE ERYTHEMA	11 (<1%)	12 (1%)	9 (1%)	32 (1%)	2 (<1%)
INJECTION SITE HAEMORRHAGE	0	1 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)
INJECTION SITE INDURATION	9 (<1%)	6 (1%)	6 (<1%)	21 (<1%)	1 (<1%)
INJECTION SITE IRRITATION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE MASS	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE OEDEMA	0	1 (<1%)	1 (<1%)	2 (<1%)	0
INJECTION SITE PAIN	6 (<1%)	9 (1%)	13 (1%)	28 (<1%)	8 (<1%)
INJECTION SITE PRURITUS	11 (<1%)	4 (<1%)	12 (1%)	27 (<1%)	5 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
GEN. DISORDERS & ADMIN. SITE COND.					
INJECTION SITE REACTION	0	0	2 (<1%)	2 (<1%)	0
INJECTION SITE SWELLING	5 (<1%)	1 (<1%)	0	6 (<1%)	0
INJECTION SITE WARMTH	3 (<1%)	2 (<1%)	4 (<1%)	9 (<1%)	3 (<1%)
IRRITABILITY	0	0	0	0	1 (<1%)
MALAISE	24 (1%)	16 (1%)	18 (1%)	58 (1%)	10 (1%)
MASS	1 (<1%)	0	0	1 (<1%)	0
OEDEMA PERIPHERAL	0	1 (<1%)	1 (<1%)	2 (<1%)	0
PAIN	8 (<1%)	0	3 (<1%)	11 (<1%)	2 (<1%)
PYREXIA	17 (<1%)	1 (<1%)	2 (<1%)	20 (<1%)	0
TEMPERATURE INTOLERANCE	1 (<1%)	0	0	1 (<1%)	0
TENDERNESS	0	0	1 (<1%)	1 (<1%)	0
THIRST	0	1 (<1%)	1 (<1%)	2 (<1%)	0
VESSEL PUNCTURE SITE HAEMATOMA	0	0	0	0	1 (<1%)
HEPATO-BILIARY DISORDERS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
BILIARY COLIC	0	1 (<1%)	0	1 (<1%)	0
HEPATITIS	1 (<1%)	0	0	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	4 (<1%)	0	2 (<1%)	6 (<1%)	2 (<1%)
ALLERGY TO ANIMAL	1 (<1%)	0	0	1 (<1%)	0
DRUG HYPERSENSITIVITY	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
IMMUNE SYSTEM DISORDERS					
HYPERSENSITIVITY	3 (<1%)	0	1 (<1%)	4 (<1%)	0
MULTIPLE ALLERGIES	0	0	1 (<1%)	1 (<1%)	0
SEASONAL ALLERGY	0	0	0	0	1 (<1%)
INFECTIONS & INFESTATIONS	150 (4%)	61 (5%)	79 (5%)	290 (5%)	103 (6%)
ABDOMINAL ABSCESS	0	0	0	0	1 (<1%)
ABSCESS	1 (<1%)	0	0	1 (<1%)	0
ABSCESS LIMB	0	1 (<1%)	0	1 (<1%)	0
ABSCESS ORAL	0	0	1 (<1%)	1 (<1%)	0
ACUTE SINUSITIS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
ACUTE TONSILLITIS	0	1 (<1%)	0	1 (<1%)	0
BACTERIAL INFECTION	0	0	1 (<1%)	1 (<1%)	0
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION	1 (<1%)	0	0	1 (<1%)	0
BODY TINEA	1 (<1%)	0	0	1 (<1%)	0
BREAST CELLULITIS	0	0	0	0	1 (<1%)
BRONCHITIS	4 (<1%)	1 (<1%)	3 (<1%)	8 (<1%)	6 (<1%)
BRONCHITIS VIRAL	1 (<1%)	0	0	1 (<1%)	0
BRONCHOPNEUMONIA	0	1 (<1%)	0	1 (<1%)	0
CELLULITIS	4 (<1%)	1 (<1%)	0	5 (<1%)	0
CONJUNCTIVITIS BACTERIAL	0	0	0	0	1 (<1%)
CYSTITIS	0	0	1 (<1%)	1 (<1%)	2 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
EAR INFECTION	4 (<1%)	2 (<1%)	2 (<1%)	8 (<1%)	0
EAR LOBE INFECTION	1 (<1%)	0	0	1 (<1%)	0
ENTEROBIASIS	0	0	0	0	1 (<1%)
EYE INFECTION	1 (<1%)	0	0	1 (<1%)	0
FUNGAL INFECTION	1 (<1%)	1 (<1%)	0	2 (<1%)	3 (<1%)
FUNGAL SKIN INFECTION	0	0	0	0	2 (<1%)
GASTROENTERITIS	4 (<1%)	3 (<1%)	4 (<1%)	11 (<1%)	7 (<1%)
GASTROENTERITIS VIRAL	4 (<1%)	0	2 (<1%)	6 (<1%)	2 (<1%)
HELICOBACTER INFECTION	0	0	1 (<1%)	1 (<1%)	0
HERPES ZOSTER	0	0	0	0	1 (<1%)
HORDEOLUM	0	1 (<1%)	0	1 (<1%)	0
IMPETIGO	2 (<1%)	0	0	2 (<1%)	0
INFECTION PARASITIC	0	0	0	0	1 (<1%)
INFECTIOUS MONONUCLEOSIS	2 (<1%)	0	0	2 (<1%)	0
INFLUENZA	7 (<1%)	2 (<1%)	1 (<1%)	10 (<1%)	2 (<1%)
INJECTION SITE INFECTION	0	0	1 (<1%)	1 (<1%)	0
LARYNGITIS	1 (<1%)	0	0	1 (<1%)	1 (<1%)
LATENT TUBERCULOSIS	0	0	0	0	1 (<1%)
MASTITIS	0	0	1 (<1%)	1 (<1%)	0
MOLLUSCUM CONTAGIOSUM	1 (<1%)	0	0	1 (<1%)	0
MYCOPLASMA INFECTION	2 (<1%)	0	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
NAIL BED INFECTION	1 (<1%)	0	0	1 (<1%)	1 (<1%)
NASOPHARYNGITIS	17 (<1%)	17 (1%)	13 (1%)	47 (1%)	15 (1%)
OMPHALITIS	0	1 (<1%)	0	1 (<1%)	0
ONYCHOMYCOSIS	0	0	0	0	1 (<1%)
ORAL HERPES	1 (<1%)	2 (<1%)	2 (<1%)	5 (<1%)	5 (<1%)
OTITIS EXTERNA	0	0	0	0	4 (<1%)
OTITIS MEDIA	4 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
OTITIS MEDIA ACUTE	1 (<1%)	0	0	1 (<1%)	0
PELVIC INFLAMMATORY DISEASE	0	2 (<1%)	0	2 (<1%)	1 (<1%)
PERTUSSIS	0	1 (<1%)	0	1 (<1%)	0
PHARYNGITIS	20 (1%)	3 (<1%)	7 (<1%)	30 (<1%)	5 (<1%)
PHARYNGITIS BACTERIAL	0	0	0	0	1 (<1%)
PHARYNGITIS STREPTOCOCCAL	10 (<1%)	0	2 (<1%)	12 (<1%)	4 (<1%)
PNEUMONIA	0	0	0	0	1 (<1%)
POSTOPERATIVE WOUND INFECTION	0	0	0	0	1 (<1%)
RESPIRATORY TRACT INFECTION	0	0	1 (<1%)	1 (<1%)	0
RESPIRATORY TRACT INFECTION VIRAL	1 (<1%)	0	0	1 (<1%)	0
RHINITIS	4 (<1%)	2 (<1%)	9 (1%)	15 (<1%)	5 (<1%)
SINUSITIS	13 (<1%)	4 (<1%)	3 (<1%)	20 (<1%)	6 (<1%)
SYPHILIS	0	0	0	0	1 (<1%)
TINEA CRURIS	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
TINEA PEDIS	1 (<1%)	0	0	1 (<1%)	0
TONSILLITIS	8 (<1%)	1 (<1%)	1 (<1%)	10 (<1%)	0
TOOTH ABSCESS	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
TOOTH INFECTION	0	0	3 (<1%)	3 (<1%)	2 (<1%)
UPPER RESPIRATORY TRACT INFECTION	29 (1%)	4 (<1%)	3 (<1%)	36 (1%)	12 (1%)
URINARY TRACT INFECTION	2 (<1%)	1 (<1%)	7 (<1%)	10 (<1%)	7 (<1%)
VAGINAL INFECTION	0	1 (<1%)	1 (<1%)	2 (<1%)	0
VAGINITIS BACTERIAL	0	0	0	0	1 (<1%)
VARICELLA	1 (<1%)	0	0	1 (<1%)	0
VIRAEMIA	1 (<1%)	0	0	1 (<1%)	0
VIRAL INFECTION	3 (<1%)	3 (<1%)	6 (<1%)	12 (<1%)	3 (<1%)
VIRAL PHARYNGITIS	0	3 (<1%)	0	3 (<1%)	2 (<1%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	0	1 (<1%)	0
VULVOVAGINAL MYCOTIC INFECTION	0	0	2 (<1%)	2 (<1%)	0
WOUND INFECTION	0	0	1 (<1%)	1 (<1%)	0
INJURY & POISONING	58 (2%)	5 (<1%)	7 (<1%)	70 (1%)	24 (1%)
ACCIDENTAL NEEDLE STICK	0	1 (<1%)	0	1 (<1%)	0
ALCOHOL POISONING	1 (<1%)	0	0	1 (<1%)	0
ANIMAL BITE	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
ANKLE FRACTURE	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - AESUM_ACWY_M1

Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INJURY & POISONING					
ARTHROPOD BITE	5 (<1%)	0	0	5 (<1%)	0
ARTHROPOD STING	1 (<1%)	0	0	1 (<1%)	0
BACK INJURY	3 (<1%)	0	0	3 (<1%)	0
CONCUSSION	2 (<1%)	0	0	2 (<1%)	1 (<1%)
CONTUSION	1 (<1%)	0	1 (<1%)	2 (<1%)	0
EPICONDYLITIS	0	0	0	0	1 (<1%)
EXCORIATION	5 (<1%)	0	0	5 (<1%)	1 (<1%)
EYE INJURY	1 (<1%)	0	0	1 (<1%)	0
FACE INJURY	1 (<1%)	0	0	1 (<1%)	0
FALL	0	0	0	0	1 (<1%)
FOOT FRACTURE	2 (<1%)	0	0	2 (<1%)	0
HAND FRACTURE	2 (<1%)	0	0	2 (<1%)	0
HEAD INJURY	0	0	1 (<1%)	1 (<1%)	0
HEAT EXHAUSTION	0	0	1 (<1%)	1 (<1%)	0
INJURY	1 (<1%)	2 (<1%)	0	3 (<1%)	3 (<1%)
JOINT DISLOCATION	0	0	0	0	1 (<1%)
JOINT INJURY	3 (<1%)	0	0	3 (<1%)	2 (<1%)
JOINT SPRAIN	9 (<1%)	0	2 (<1%)	11 (<1%)	3 (<1%)
LIMB INJURY	4 (<1%)	0	0	4 (<1%)	0
MOUTH INJURY	0	0	0	0	1 (<1%)
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INJURY & POISONING					
MULTIPLE INJURIES	0	0	0	0	1 (<1%)
MUSCLE STRAIN	2 (<1%)	1 (<1%)	0	3 (<1%)	1 (<1%)
NECK INJURY	2 (<1%)	0	0	2 (<1%)	0
PROCEDURAL PAIN	2 (<1%)	0	1 (<1%)	3 (<1%)	1 (<1%)
RADIUS FRACTURE	1 (<1%)	0	0	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	1 (<1%)	2 (<1%)	0
SKIN LACERATION	3 (<1%)	0	0	3 (<1%)	2 (<1%)
SPLINTER	0	0	0	0	1 (<1%)
SPORTS INJURY	1 (<1%)	0	0	1 (<1%)	0
SUNBURN	0	0	0	0	2 (<1%)
THERMAL BURN	2 (<1%)	0	0	2 (<1%)	0
TIBIA FRACTURE	1 (<1%)	0	0	1 (<1%)	0
TRAUMATIC TORTICOLLIS	1 (<1%)	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	1 (<1%)	0	0	1 (<1%)	0
VACCINATION COMPLICATION	1 (<1%)	0	0	1 (<1%)	0
WHIPLASH INJURY	1 (<1%)	0	0	1 (<1%)	0
WOUND	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
WRIST FRACTURE	1 (<1%)	0	0	1 (<1%)	0
INVESTIGATIONS	1 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
BLOOD POTASSIUM DECREASED	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INVESTIGATIONS					
BLOOD PRESSURE INCREASED	0	0	1 (<1%)	1 (<1%)	0
TUBERCULOSIS SKIN TEST POSITIVE	1 (<1%)	0	0	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	6 (<1%)	0	0	6 (<1%)	3 (<1%)
ANOREXIA	3 (<1%)	0	0	3 (<1%)	0
DEHYDRATION	1 (<1%)	0	0	1 (<1%)	0
DYSLIPIDAEMIA	0	0	0	0	1 (<1%)
HYPERCHOLESTEROLAEMIA	1 (<1%)	0	0	1 (<1%)	0
INCREASED APPETITE	0	0	0	0	2 (<1%)
METABOLIC ACIDOSIS	1 (<1%)	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	46 (1%)	22 (2%)	60 (4%)	128 (2%)	61 (3%)
ARTHRALGIA	14 (<1%)	7 (1%)	15 (1%)	36 (1%)	16 (1%)
BACK PAIN	7 (<1%)	6 (1%)	16 (1%)	29 (<1%)	10 (1%)
BURSITIS	1 (<1%)	0	0	1 (<1%)	0
COSTOCHONDRITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
EXOSTOSIS	1 (<1%)	0	0	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (<1%)
JOINT HYPEREXTENSION	0	0	1 (<1%)	1 (<1%)	0
JOINT STIFFNESS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
MEDIAL TIBIAL STRESS SYNDROME	0	0	1 (<1%)	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
MUSCULO., CONNECT. TIS. & BONE DIS.					
MUSCLE CONTRACTURE	0	0	1 (<1%)	1 (<1%)	0
MUSCLE SPASMS	3 (<1%)	1 (<1%)	3 (<1%)	7 (<1%)	6 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
MUSCULOSKELETAL CHEST PAIN	0	0	0	0	1 (<1%)
MUSCULOSKELETAL PAIN	0	0	2 (<1%)	2 (<1%)	3 (<1%)
MUSCULOSKELETAL STIFFNESS	0	0	1 (<1%)	1 (<1%)	2 (<1%)
MYALGIA	11 (<1%)	8 (1%)	17 (1%)	36 (1%)	12 (1%)
NECK PAIN	1 (<1%)	2 (<1%)	5 (<1%)	8 (<1%)	1 (<1%)
OSTEOCHONDROSIS	0	0	1 (<1%)	1 (<1%)	0
PAIN IN EXTREMITY	9 (<1%)	2 (<1%)	9 (1%)	20 (<1%)	15 (1%)
PAIN IN JAW	1 (<1%)	0	0	1 (<1%)	0
RHABDOMYOLYSIS	1 (<1%)	0	0	1 (<1%)	0
SPINAL DEFORMITY	0	0	1 (<1%)	1 (<1%)	0
TENDONITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
TORTICOLLIS	1 (<1%)	0	0	1 (<1%)	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	2 (<1%)	0	2 (<1%)	4 (<1%)	1 (<1%)
FIBROADENOMA OF BREAST	1 (<1%)	0	0	1 (<1%)	0
PITUITARY TUMOUR BENIGN	1 (<1%)	0	0	1 (<1%)	0
POLYCYTHAEMIA VERA	0	0	1 (<1%)	1 (<1%)	0
SKIN PAPILLOMA	0	0	0	0	1 (<1%)
UTERINE LEIOMYOMA	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
NERVOUS SYSTEM DISORDERS	74 (2%)	48 (4%)	50 (3%)	172 (3%)	69 (4%)
BURNING SENSATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CARPAL TUNNEL SYNDROME	0	0	0	0	2 (<1%)
DISTURBANCE IN ATTENTION	1 (<1%)	0	0	1 (<1%)	0
DIZZINESS	7 (<1%)	8 (1%)	6 (<1%)	21 (<1%)	16 (1%)
ENCEPHALOPATHY	1 (<1%)	0	0	1 (<1%)	0
FACIAL NEURALGIA	1 (<1%)	0	0	1 (<1%)	0
HEADACHE	58 (2%)	29 (3%)	31 (2%)	118 (2%)	37 (2%)
HYPOAESTHESIA	2 (<1%)	0	0	2 (<1%)	0
MIGRAINE	0	6 (1%)	3 (<1%)	9 (<1%)	1 (<1%)
MUSCLE CONTRACTIONS INVOLUNTARY	0	1 (<1%)	0	1 (<1%)	0
NEURALGIA	0	0	0	0	1 (<1%)
PARAESTHESIA	1 (<1%)	2 (<1%)	4 (<1%)	7 (<1%)	4 (<1%)
SCIATICA	0	0	1 (<1%)	1 (<1%)	2 (<1%)
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	0	1 (<1%)	0
SINUS HEADACHE	1 (<1%)	1 (<1%)	6 (<1%)	8 (<1%)	1 (<1%)
SOMNOLENCE	2 (<1%)	3 (<1%)	2 (<1%)	7 (<1%)	2 (<1%)
SYNCOPE	2 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)
SYNCOPE VASOVAGAL	0	2 (<1%)	0	2 (<1%)	1 (<1%)
PSYCHIATRIC DISORDERS	12 (<1%)	4 (<1%)	8 (1%)	24 (<1%)	8 (<1%)
AGGRESSION	1 (<1%)	0	0	1 (<1%)	0
ANXIETY	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	 Ages 19-34 (N=1145)	 Ages 35-55 (N=1461)	 Total ACWY (N=6185)	 Total Menactra (N=1757)
...Continued from previous page					
PSYCHIATRIC DISORDERS					
BIPOLAR DISORDER	1 (<1%)	0	0	1 (<1%)	0
DEPRESSION	4 (<1%)	1 (<1%)	3 (<1%)	8 (<1%)	4 (<1%)
DEPRESSION SUICIDAL	1 (<1%)	0	0	1 (<1%)	0
INSOMNIA	3 (<1%)	2 (<1%)	3 (<1%)	8 (<1%)	3 (<1%)
POST-TRAUMATIC STRESS DISORDER	0	0	1 (<1%)	1 (<1%)	0
RESTLESSNESS	0	0	1 (<1%)	1 (<1%)	0
STRESS	2 (<1%)	0	0	2 (<1%)	0
RENAL & URINARY DISORDERS	0	1 (<1%)	2 (<1%)	3 (<1%)	0
CALCULUS URETERIC	0	0	1 (<1%)	1 (<1%)	0
NEPHROLITHIASIS	0	1 (<1%)	1 (<1%)	2 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	37 (1%)	13 (1%)	7 (<1%)	57 (1%)	11 (1%)
ADNEXA UTERI PAIN	5 (<1%)	0	0	5 (<1%)	0
BREAST PAIN	0	0	0	0	1 (<1%)
DYSMENORRHOEA	30 (1%)	13 (1%)	6 (<1%)	49 (1%)	5 (<1%)
GYNAECOMASTIA	1 (<1%)	0	0	1 (<1%)	0
OLIGOMENORRHOEA	0	0	1 (<1%)	1 (<1%)	0
OVULATION PAIN	1 (<1%)	0	0	1 (<1%)	0
POSTMENOPAUSAL HAEMORRHAGE	0	0	0	0	1 (<1%)
PREMENSTRUAL SYNDROME	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
REPRODUCT. SYS. & BREAST DISORDERS					
VAGINAL DISCHARGE	0	0	0	0	2 (<1%)
VULVOVAGINAL BURNING SENSATION	0	0	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	89 (2%)	14 (1%)	30 (2%)	133 (2%)	31 (2%)
ASTHMA	3 (<1%)	0	0	3 (<1%)	0
BRONCHIAL HYPERREACTIVITY	0	1 (<1%)	0	1 (<1%)	0
COUGH	26 (1%)	3 (<1%)	4 (<1%)	33 (1%)	4 (<1%)
DRY THROAT	0	0	1 (<1%)	1 (<1%)	0
DYSPHONIA	0	1 (<1%)	0	1 (<1%)	0
DYSPNOEA	1 (<1%)	2 (<1%)	0	3 (<1%)	1 (<1%)
EPISTAXIS	3 (<1%)	0	3 (<1%)	6 (<1%)	2 (<1%)
NASAL CONGESTION	15 (<1%)	2 (<1%)	4 (<1%)	21 (<1%)	5 (<1%)
NASAL DRYNESS	0	0	1 (<1%)	1 (<1%)	0
PARANASAL SINUS HYPERSECRETION	1 (<1%)	0	0	1 (<1%)	1 (<1%)
PHARYNGEAL OEDEMA	1 (<1%)	0	0	1 (<1%)	0
PHARYNGOLARYNGEAL PAIN	32 (1%)	7 (1%)	12 (1%)	51 (1%)	15 (1%)
PULMONARY CONGESTION	3 (<1%)	0	0	3 (<1%)	2 (<1%)
RESPIRATORY DISORDER	0	0	0	0	1 (<1%)
RHINITIS ALLERGIC	4 (<1%)	1 (<1%)	4 (<1%)	9 (<1%)	4 (<1%)
RHINORRHOEA	7 (<1%)	1 (<1%)	2 (<1%)	10 (<1%)	2 (<1%)
SINUS CONGESTION	7 (<1%)	1 (<1%)	1 (<1%)	9 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
RESP., THORACIC & MEDIASTINAL DIS.					
SNEEZING	1 (<1%)	0	0	1 (<1%)	0
THROAT IRRITATION	1 (<1%)	0	1 (<1%)	2 (<1%)	0
TONSILLAR DISORDER	1 (<1%)	0	0	1 (<1%)	0
TONSILLAR HYPERTROPHY	1 (<1%)	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	44 (1%)	8 (1%)	20 (1%)	72 (1%)	30 (2%)
ACNE	4 (<1%)	0	0	4 (<1%)	2 (<1%)
ALOPECIA	0	0	0	0	1 (<1%)
ANGIOEDEMA	1 (<1%)	0	0	1 (<1%)	1 (<1%)
DERMAL CYST	1 (<1%)	1 (<1%)	0	2 (<1%)	0
DERMATITIS ALLERGIC	2 (<1%)	0	1 (<1%)	3 (<1%)	0
DERMATITIS ATOPIC	0	0	0	0	1 (<1%)
DERMATITIS CONTACT	12 (<1%)	0	1 (<1%)	13 (<1%)	4 (<1%)
DRY SKIN	0	0	0	0	1 (<1%)
ECCHYMOSIS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
ERYTHEMA	6 (<1%)	1 (<1%)	9 (1%)	16 (<1%)	4 (<1%)
HYPERHIDROSIS	0	0	2 (<1%)	2 (<1%)	3 (<1%)
HYPOAESTHESIA FACIAL	1 (<1%)	0	0	1 (<1%)	0
INGROWING NAIL	2 (<1%)	0	0	2 (<1%)	1 (<1%)
PETECHIAE	1 (<1%)	0	0	1 (<1%)	0
PITYRIASIS ROSEA	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 32

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
SKIN & SUBCUTANEOUS TIS. DISORDERS					
PRURIGO	0	0	0	0	1 (<1%)
PRURITUS	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
PRURITUS GENERALISED	0	0	1 (<1%)	1 (<1%)	0
RASH	10 (<1%)	4 (<1%)	6 (<1%)	20 (<1%)	6 (<1%)
RASH MACULAR	0	0	0	0	1 (<1%)
SKIN DISCOLOURATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
URTICARIA	1 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	7 (<1%)	0	0	7 (<1%)	0
ENDODONTIC PROCEDURE	1 (<1%)	0	0	1 (<1%)	0
FINGER AMPUTATION	1 (<1%)	0	0	1 (<1%)	0
TOOTH EXTRACTION	2 (<1%)	0	0	2 (<1%)	0
WISDOM TEETH REMOVAL	3 (<1%)	0	0	3 (<1%)	0
VASCULAR DISORDERS	0	1 (<1%)	6 (<1%)	7 (<1%)	6 (<1%)
FLUSHING	0	0	2 (<1%)	2 (<1%)	2 (<1%)
HYPERTENSION	0	1 (<1%)	4 (<1%)	5 (<1%)	2 (<1%)
HYPERTENSIVE CRISIS	0	0	0	0	1 (<1%)
HYPOTENSION	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 33.1

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	472 (18%)	114 (13%)	586 (16%)	109 (20%)	49 (23%)	93 (10%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	6 (<1%)	0	6 (<1%)	0	1 (<1%)	2 (<1%)
LYMPHADENOPATHY	6 (<1%)	0	6 (<1%)	0	0	2 (<1%)
SPLENOMEGALY	0	0	0	0	1 (<1%)	0
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	1 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	7 (<1%)	2 (<1%)	9 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
AURICULAR SWELLING	1 (<1%)	0	1 (<1%)	0	0	0
EAR PAIN	4 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
MOTION SICKNESS	0	1 (<1%)	1 (<1%)	0	0	0
VERTIGO	2 (<1%)	0	2 (<1%)	0	0	0
ENDOCRINE DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
CUSHING'S SYNDROME	0	1 (<1%)	1 (<1%)	0	0	0
EYE DISORDERS	7 (<1%)	0	7 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
CONJUNCTIVITIS	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
EYE ALLERGY	1 (<1%)	0	1 (<1%)	0	0	0
EYE PAIN	2 (<1%)	0	2 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.1

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
EYE DISORDERS						
EYE PRURITUS	0	0	0	1 (<1%)	0	0
EYE SWELLING	0	0	0	0	0	1 (<1%)
OCULAR HYPERAEMIA	1 (<1%)	0	1 (<1%)	0	0	0
VISION BLURRED	0	0	0	0	1 (<1%)	0
GASTROINTESTINAL DISORDERS	71 (3%)	23 (3%)	94 (3%)	17 (3%)	6 (3%)	19 (2%)
ABDOMINAL PAIN	6 (<1%)	5 (1%)	11 (<1%)	1 (<1%)	0	6 (1%)
ABDOMINAL PAIN UPPER	12 (<1%)	4 (<1%)	16 (<1%)	2 (<1%)	0	1 (<1%)
APHTHOUS STOMATITIS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
COLITIS	0	1 (<1%)	1 (<1%)	0	0	0
CONSTIPATION	0	0	0	0	1 (<1%)	0
DIARRHOEA	12 (<1%)	4 (<1%)	16 (<1%)	7 (1%)	0	1 (<1%)
ENTEROCOLITIS	0	1 (<1%)	1 (<1%)	0	0	0
GASTRITIS	1 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	0	0	0	1 (<1%)	0	1 (<1%)
GINGIVAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
GINGIVITIS	1 (<1%)	0	1 (<1%)	0	0	0
HYPERCHLORHYDRIA	1 (<1%)	0	1 (<1%)	0	0	0
NAUSEA	22 (1%)	3 (<1%)	25 (1%)	2 (<1%)	2 (1%)	5 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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...Continued from previous page						
GASTROINTESTINAL DISORDERS						
ODYNOPHAGIA	0	0	0	0	0	2 (<1%)
ORAL PAIN	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
RECTAL HAEMORRHAGE	1 (<1%)	0	1 (<1%)	0	0	0
STOMACH DISCOMFORT	1 (<1%)	0	1 (<1%)	0	0	0
STOMATITIS	1 (<1%)	0	1 (<1%)	0	0	0
TOOTHACHE	6 (<1%)	3 (<1%)	9 (<1%)	1 (<1%)	0	0
VOMITING	16 (1%)	2 (<1%)	18 (1%)	4 (1%)	3 (1%)	2 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	88 (3%)	18 (2%)	106 (3%)	13 (2%)	7 (3%)	18 (2%)
ASTHENIA	4 (<1%)	0	4 (<1%)	0	0	0
AXILLARY PAIN	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
CHEST DISCOMFORT	2 (<1%)	0	2 (<1%)	0	0	0
CHEST PAIN	3 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)
CHILLS	6 (<1%)	0	6 (<1%)	0	1 (<1%)	2 (<1%)
FATIGUE	4 (<1%)	0	4 (<1%)	1 (<1%)	0	0
FEELING HOT	1 (<1%)	0	1 (<1%)	0	0	0
HUNGER	1 (<1%)	0	1 (<1%)	0	0	0
INDURATION	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	0	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	1 (<1%)	0	0	0

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...Continued from previous page						
GEN. DISORDERS & ADMIN. SITE COND.						
INJECTION SITE ANAESTHESIA	0	0	0	1 (<1%)	0	0
INJECTION SITE BRUISING	4 (<1%)	0	4 (<1%)	1 (<1%)	1 (<1%)	0
INJECTION SITE ERYTHEMA	10 (<1%)	1 (<1%)	11 (<1%)	1 (<1%)	0	1 (<1%)
INJECTION SITE INDURATION	7 (<1%)	2 (<1%)	9 (<1%)	0	0	2 (<1%)
INJECTION SITE PAIN	6 (<1%)	0	6 (<1%)	2 (<1%)	0	1 (<1%)
INJECTION SITE PRURITUS	11 (<1%)	0	11 (<1%)	1 (<1%)	0	0
INJECTION SITE SWELLING	5 (<1%)	0	5 (<1%)	0	0	1 (<1%)
INJECTION SITE WARMTH	3 (<1%)	0	3 (<1%)	0	0	0
IRRITABILITY	0	0	0	1 (<1%)	0	0
MALAISE	19 (1%)	5 (1%)	24 (1%)	3 (1%)	4 (2%)	6 (1%)
MASS	1 (<1%)	0	1 (<1%)	0	0	0
PAIN	5 (<1%)	3 (<1%)	8 (<1%)	0	0	1 (<1%)
PYREXIA	9 (<1%)	8 (1%)	17 (<1%)	0	1 (<1%)	7 (1%)
TEMPERATURE INTOLERANCE	1 (<1%)	0	1 (<1%)	0	0	0
TENDERNESS	0	0	0	0	1 (<1%)	0
VESSEL PUNCTURE SITE HAEMATOMA	0	0	0	1 (<1%)	0	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
HEPATITIS	1 (<1%)	0	1 (<1%)	0	0	0

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IMMUNE SYSTEM DISORDERS	2 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
ALLERGY TO ANIMAL	1 (<1%)	0	1 (<1%)	0	0	0
ATOPY	0	0	0	0	0	1 (<1%)
HOUSE DUST ALLERGY	0	0	0	0	0	1 (<1%)
HYPERSENSITIVITY	1 (<1%)	2 (<1%)	3 (<1%)	0	0	1 (<1%)
SEASONAL ALLERGY	0	0	0	1 (<1%)	1 (<1%)	0
INFECTIONS & INFESTATIONS	113 (4%)	37 (4%)	150 (4%)	29 (5%)	20 (10%)	24 (3%)
ABDOMINAL ABSCESS	0	0	0	1 (<1%)	0	0
ABSCESS	1 (<1%)	0	1 (<1%)	0	0	0
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
BODY TINEA	1 (<1%)	0	1 (<1%)	0	0	0
BRONCHITIS	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	1 (<1%)	0
BRONCHITIS VIRAL	1 (<1%)	0	1 (<1%)	0	0	0
CELLULITIS	3 (<1%)	1 (<1%)	4 (<1%)	0	0	0
EAR INFECTION	2 (<1%)	2 (<1%)	4 (<1%)	0	0	0
EAR LOBE INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
ENTEROBIASIS	0	0	0	1 (<1%)	0	0
EYE INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
FUNGAL INFECTION	0	1 (<1%)	1 (<1%)	0	0	0
GASTROENTERITIS	4 (<1%)	0	4 (<1%)	2 (<1%)	0	2 (<1%)
GASTROENTERITIS VIRAL	4 (<1%)	0	4 (<1%)	1 (<1%)	0	0

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...Continued from previous page						
INFECTIONS & INFESTATIONS						
IMPETIGO	2 (<1%)	0	2 (<1%)	0	0	0
INFECTIOUS MONONUCLEOSIS	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0
INFLUENZA	5 (<1%)	2 (<1%)	7 (<1%)	0	1 (<1%)	3 (<1%)
LARYNGITIS	1 (<1%)	0	1 (<1%)	0	0	0
LATENT TUBERCULOSIS	0	0	0	1 (<1%)	0	0
MOLLUSCUM CONTAGIOSUM	1 (<1%)	0	1 (<1%)	0	0	0
MYCOPLASMA INFECTION	2 (<1%)	0	2 (<1%)	0	0	0
NAIL BED INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
NASOPHARYNGITIS	10 (<1%)	7 (1%)	17 (<1%)	3 (1%)	3 (1%)	5 (1%)
ORAL HERPES	1 (<1%)	0	1 (<1%)	0	0	0
OTITIS EXTERNA	0	0	0	3 (1%)	1 (<1%)	0
OTITIS MEDIA	4 (<1%)	0	4 (<1%)	0	1 (<1%)	0
OTITIS MEDIA ACUTE	1 (<1%)	0	1 (<1%)	0	0	0
PELVIC INFLAMMATORY DISEASE	0	0	0	1 (<1%)	0	0
PHARYNGITIS	13 (<1%)	7 (1%)	20 (1%)	0	5 (2%)	2 (<1%)
PHARYNGITIS STREPTOCOCCAL	10 (<1%)	0	10 (<1%)	2 (<1%)	1 (<1%)	0
PHARYNGOTONSILLITIS	0	0	0	0	0	1 (<1%)
PNEUMONIA	0	0	0	1 (<1%)	0	0
PNEUMONIA PRIMARY ATYPICAL	0	0	0	0	1 (<1%)	0

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...Continued from previous page						
INFECTIONS & INFESTATIONS						
RESPIRATORY TRACT INFECTION VIRAL	1 (<1%)	0	1 (<1%)	0	0	0
RHINITIS	1 (<1%)	3 (<1%)	4 (<1%)	0	0	3 (<1%)
SINUSITIS	13 (<1%)	0	13 (<1%)	1 (<1%)	2 (1%)	2 (<1%)
TINEA INFECTION	0	0	0	0	1 (<1%)	0
TINEA PEDIS	1 (<1%)	0	1 (<1%)	0	0	0
TONSILLITIS	4 (<1%)	4 (<1%)	8 (<1%)	0	0	4 (<1%)
TOOTH ABSCESS	0	1 (<1%)	1 (<1%)	0	0	0
UPPER RESPIRATORY TRACT INFECTION	19 (1%)	10 (1%)	29 (1%)	7 (1%)	3 (1%)	2 (<1%)
URINARY TRACT INFECTION	2 (<1%)	0	2 (<1%)	1 (<1%)	0	0
VARICELLA	1 (<1%)	0	1 (<1%)	0	0	0
VIRAEMIA	1 (<1%)	0	1 (<1%)	0	0	0
VIRAL INFECTION	3 (<1%)	0	3 (<1%)	2 (<1%)	1 (<1%)	0
VIRAL PHARYNGITIS	0	0	0	1 (<1%)	1 (<1%)	0
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
INJURY & POISONING	57 (2%)	1 (<1%)	58 (2%)	17 (3%)	3 (1%)	6 (1%)
ALCOHOL POISONING	1 (<1%)	0	1 (<1%)	0	0	0
ANIMAL BITE	1 (<1%)	0	1 (<1%)	2 (<1%)	0	0
ANKLE FRACTURE	0	0	0	1 (<1%)	0	0

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...Continued from previous page						
INJURY & POISONING						
ARTHROPOD BITE	4 (<1%)	1 (<1%)	5 (<1%)	0	0	0
ARTHROPOD STING	1 (<1%)	0	1 (<1%)	0	0	0
BACK INJURY	3 (<1%)	0	3 (<1%)	0	0	0
CONCUSSION	2 (<1%)	0	2 (<1%)	1 (<1%)	1 (<1%)	0
CONTUSION	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
EPICONDYLITIS	0	0	0	1 (<1%)	0	0
EXCORIATION	5 (<1%)	0	5 (<1%)	1 (<1%)	0	0
EYE INJURY	1 (<1%)	0	1 (<1%)	0	0	0
FACE INJURY	1 (<1%)	0	1 (<1%)	0	0	0
FOOT FRACTURE	2 (<1%)	0	2 (<1%)	0	0	0
HAND FRACTURE	2 (<1%)	0	2 (<1%)	0	0	0
INJURY	1 (<1%)	0	1 (<1%)	1 (<1%)	0	3 (<1%)
JOINT DISLOCATION	0	0	0	1 (<1%)	0	0
JOINT INJURY	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
JOINT SPRAIN	9 (<1%)	0	9 (<1%)	2 (<1%)	0	1 (<1%)
LIMB INJURY	4 (<1%)	0	4 (<1%)	0	0	1 (<1%)
MOUTH INJURY	0	0	0	1 (<1%)	0	0
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	1 (<1%)	0	0	0
MUSCLE STRAIN	2 (<1%)	0	2 (<1%)	1 (<1%)	0	0

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...Continued from previous page						
INJURY & POISONING						
NECK INJURY	2 (<1%)	0	2 (<1%)	0	0	0
PROCEDURAL PAIN	2 (<1%)	0	2 (<1%)	1 (<1%)	0	0
RADIUS FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	1 (<1%)	0	0	0
SKIN LACERATION	3 (<1%)	0	3 (<1%)	1 (<1%)	1 (<1%)	0
SPLINTER	0	0	0	1 (<1%)	0	0
SPORTS INJURY	1 (<1%)	0	1 (<1%)	0	0	0
SUNBURN	0	0	0	1 (<1%)	0	0
THERMAL BURN	2 (<1%)	0	2 (<1%)	0	0	0
TIBIA FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
TRAUMATIC TORTICOLLIS	1 (<1%)	0	1 (<1%)	0	0	0
UPPER LIMB FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
VACCINATION COMPLICATION	1 (<1%)	0	1 (<1%)	0	0	0
WHIPLASH INJURY	1 (<1%)	0	1 (<1%)	0	0	0
WOUND	1 (<1%)	0	1 (<1%)	0	0	0
WRIST FRACTURE	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
INVESTIGATIONS	1 (<1%)	0	1 (<1%)	0	0	0
TUBERCULOSIS SKIN TEST POSITIVE	1 (<1%)	0	1 (<1%)	0	0	0

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METABOLISM & NUTRITION DISORDERS	6 (<1%)	0	6 (<1%)	1 (<1%)	0	0
ANOREXIA	3 (<1%)	0	3 (<1%)	0	0	0
DEHYDRATION	1 (<1%)	0	1 (<1%)	0	0	0
DYSLIPIDAEMIA	0	0	0	1 (<1%)	0	0
HYPERCHOLESTEROLAEMIA	1 (<1%)	0	1 (<1%)	0	0	0
METABOLIC ACIDOSIS	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	42 (2%)	4 (<1%)	46 (1%)	10 (2%)	4 (2%)	8 (1%)
ARTHRALGIA	13 (<1%)	1 (<1%)	14 (<1%)	3 (1%)	0	2 (<1%)
BACK PAIN	6 (<1%)	1 (<1%)	7 (<1%)	0	0	1 (<1%)
BURSITIS	1 (<1%)	0	1 (<1%)	0	0	0
COSTOCHONDRITIS	1 (<1%)	0	1 (<1%)	0	0	0
EXOSTOSIS	1 (<1%)	0	1 (<1%)	0	0	0
JOINT STIFFNESS	1 (<1%)	0	1 (<1%)	0	0	0
MUSCLE SPASMS	3 (<1%)	0	3 (<1%)	1 (<1%)	0	0
MUSCULAR WEAKNESS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
MUSCULOSKELETAL PAIN	0	0	0	1 (<1%)	1 (<1%)	0
MYALGIA	11 (<1%)	0	11 (<1%)	2 (<1%)	1 (<1%)	5 (1%)
NECK PAIN	1 (<1%)	0	1 (<1%)	0	2 (1%)	1 (<1%)
PAIN IN EXTREMITY	7 (<1%)	2 (<1%)	9 (<1%)	4 (1%)	1 (<1%)	0
PAIN IN JAW	1 (<1%)	0	1 (<1%)	0	0	0
RHABDOMYOLYSIS	1 (<1%)	0	1 (<1%)	0	0	0

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...Continued from previous page						
MUSCULO., CONNECT. TIS. & BONE DIS.						
TENDONITIS	1 (<1%)	0	1 (<1%)	0	0	0
TORTICOLLIS	1 (<1%)	0	1 (<1%)	0	0	0
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
FIBROADENOMA OF BREAST	1 (<1%)	0	1 (<1%)	0	0	0
PITUITARY TUMOUR BENIGN	0	1 (<1%)	1 (<1%)	0	0	0
SKIN PAPILLOMA	0	0	0	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	57 (2%)	17 (2%)	74 (2%)	17 (3%)	11 (5%)	20 (2%)
AMNESIA	0	0	0	0	0	1 (<1%)
BURNING SENSATION	0	0	0	0	0	1 (<1%)
DISTURBANCE IN ATTENTION	1 (<1%)	0	1 (<1%)	0	0	0
DIZZINESS	5 (<1%)	2 (<1%)	7 (<1%)	3 (1%)	1 (<1%)	2 (<1%)
ENCEPHALOPATHY	1 (<1%)	0	1 (<1%)	0	0	0
FACIAL NEURALGIA	0	1 (<1%)	1 (<1%)	0	0	0
HEADACHE	44 (2%)	14 (2%)	58 (2%)	9 (2%)	9 (4%)	16 (2%)
HYPOAESTHESIA	2 (<1%)	0	2 (<1%)	0	0	0
MIGRAINE	0	0	0	1 (<1%)	0	0
PARAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.1

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
NERVOUS SYSTEM DISORDERS						
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	1 (<1%)	0	0	0
SINUS HEADACHE	1 (<1%)	0	1 (<1%)	0	0	0
SOMNOLENCE	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)
SYNCOPE	2 (<1%)	0	2 (<1%)	3 (1%)	1 (<1%)	0
SYNCOPE VASOVAGAL	0	0	0	1 (<1%)	0	0
PSYCHIATRIC DISORDERS	10 (<1%)	2 (<1%)	12 (<1%)	3 (1%)	0	1 (<1%)
AGGRESSION	1 (<1%)	0	1 (<1%)	0	0	0
ANXIETY	1 (<1%)	0	1 (<1%)	0	0	0
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	1 (<1%)	0	1 (<1%)	0	0	0
BIPOLAR DISORDER	1 (<1%)	0	1 (<1%)	0	0	0
DEPRESSION	4 (<1%)	0	4 (<1%)	1 (<1%)	0	0
DEPRESSION SUICIDAL	1 (<1%)	0	1 (<1%)	0	0	0
INSOMNIA	3 (<1%)	0	3 (<1%)	2 (<1%)	0	1 (<1%)
STRESS	0	2 (<1%)	2 (<1%)	0	0	0
REPRODUCT. SYS. & BREAST DISORDERS	21 (1%)	16 (2%)	37 (1%)	0	2 (1%)	7 (1%)
ADNEXA UTERI PAIN	2 (<1%)	3 (<1%)	5 (<1%)	0	0	1 (<1%)
DYSMENORRHOEA	17 (1%)	13 (1%)	30 (1%)	0	2 (1%)	6 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.1

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Subjects Ages 11-18

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...Continued from previous page						
REPRODUCT. SYS. & BREAST DISORDERS						
GYNAECOMASTIA	1 (<1%)	0	1 (<1%)	0	0	0
OVULATION PAIN	1 (<1%)	0	1 (<1%)	0	0	0
RESP., THORACIC & MEDIASTINAL DIS.	79 (3%)	10 (1%)	89 (2%)	16 (3%)	13 (6%)	9 (1%)
ASTHMA	2 (<1%)	1 (<1%)	3 (<1%)	0	0	3 (<1%)
COUGH	21 (1%)	5 (1%)	26 (1%)	1 (<1%)	4 (2%)	3 (<1%)
DYSPNOEA	1 (<1%)	0	1 (<1%)	0	0	0
EPISTAXIS	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0	0
NASAL CONGESTION	15 (1%)	0	15 (<1%)	4 (1%)	3 (1%)	1 (<1%)
PARANASAL SINUS HYPERSECRETION	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
PHARYNGEAL OEDEMA	1 (<1%)	0	1 (<1%)	0	0	0
PHARYNGOLARYNGEAL PAIN	31 (1%)	1 (<1%)	32 (1%)	8 (1%)	6 (3%)	2 (<1%)
PULMONARY CONGESTION	3 (<1%)	0	3 (<1%)	0	0	0
RESPIRATORY DISORDER	0	0	0	1 (<1%)	0	0
RHINITIS ALLERGIC	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	0	0
RHINORRHOEA	7 (<1%)	0	7 (<1%)	1 (<1%)	0	0
SINUS CONGESTION	7 (<1%)	0	7 (<1%)	0	0	0
SNEEZING	1 (<1%)	0	1 (<1%)	0	0	0
THROAT IRRITATION	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.1

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
RESP., THORACIC & MEDIASTINAL DIS.						
TONSILLAR DISORDER	0	1 (<1%)	1 (<1%)	0	0	0
TONSILLAR HYPERTROPHY	1 (<1%)	0	1 (<1%)	0	0	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	37 (1%)	7 (1%)	44 (1%)	11 (2%)	1 (<1%)	3 (<1%)
ACNE	4 (<1%)	0	4 (<1%)	1 (<1%)	0	1 (<1%)
ALOPECIA	0	0	0	1 (<1%)	0	0
ANGIOEDEMA	0	1 (<1%)	1 (<1%)	0	0	0
DERMAL CYST	1 (<1%)	0	1 (<1%)	0	0	0
DERMATITIS ALLERGIC	0	2 (<1%)	2 (<1%)	0	0	0
DERMATITIS CONTACT	12 (<1%)	0	12 (<1%)	3 (1%)	0	0
DRY SKIN	0	0	0	1 (<1%)	0	0
ERYTHEMA	4 (<1%)	2 (<1%)	6 (<1%)	1 (<1%)	0	0
HYPOAESTHESIA FACIAL	1 (<1%)	0	1 (<1%)	0	0	0
INGROWING NAIL	2 (<1%)	0	2 (<1%)	0	0	0
PETECHIAE	1 (<1%)	0	1 (<1%)	0	0	0
PITYRIASIS ROSEA	1 (<1%)	0	1 (<1%)	0	0	0
PRURITUS	2 (<1%)	0	2 (<1%)	1 (<1%)	0	0
RASH	8 (<1%)	2 (<1%)	10 (<1%)	2 (<1%)	0	0
RASH PRURITIC	0	0	0	0	0	2 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.1

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	ACWYConVax (N=899)	Total ACWY (N=3579)	Menactra (N=539)	Menomune (N=209)	Tdap (N=892)
...Continued from previous page						
SKIN & SUBCUTANEOUS TIS. DISORDERS						
SKIN DISCOLOURATION	0	0	0	1 (<1%)	0	0
URTICARIA	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
SURGICAL & MEDICAL PROCEDURES	5 (<1%)	2 (<1%)	7 (<1%)	0	0	1 (<1%)
ENDODONTIC PROCEDURE	0	1 (<1%)	1 (<1%)	0	0	0
FINGER AMPUTATION	0	1 (<1%)	1 (<1%)	0	0	0
NAIL OPERATION	0	0	0	0	0	1 (<1%)
TOOTH EXTRACTION	2 (<1%)	0	2 (<1%)	0	0	0
WISDOM TEETH REMOVAL	3 (<1%)	0	3 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	205 (18%)	101 (18%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	4 (<1%)	2 (<1%)
LYMPH NODE PAIN	1 (<1%)	0
LYMPHADENOPATHY	3 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	3 (<1%)	3 (1%)
EAR PAIN	1 (<1%)	1 (<1%)
MOTION SICKNESS	0	1 (<1%)
VERTIGO	2 (<1%)	1 (<1%)
EYE DISORDERS	3 (<1%)	1 (<1%)
BLEPHARITIS	0	1 (<1%)
CONJUNCTIVITIS	2 (<1%)	0
EYE IRRITATION	1 (<1%)	0
GASTROINTESTINAL DISORDERS	44 (4%)	25 (4%)
ABDOMINAL PAIN	6 (1%)	7 (1%)
ABDOMINAL PAIN UPPER	6 (1%)	0
CONSTIPATION	1 (<1%)	0
DIARRHOEA	12 (1%)	6 (1%)
DRY MOUTH	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
GASTROINTESTINAL DISORDERS		
DYSPEPSIA	2 (<1%)	1 (<1%)
FOOD POISONING	1 (<1%)	0
GASTRITIS	2 (<1%)	2 (<1%)
GINGIVAL PAIN	1 (<1%)	0
HYPERCHLORHYDRIA	1 (<1%)	0
LIP OEDEMA	0	1 (<1%)
NAUSEA	12 (1%)	4 (1%)
ODYNOPHAGIA	1 (<1%)	1 (<1%)
STOMACH DISCOMFORT	1 (<1%)	2 (<1%)
TOOTHACHE	2 (<1%)	1 (<1%)
VOMITING	1 (<1%)	3 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	47 (4%)	12 (2%)
APPLICATION SITE PRURITUS	0	1 (<1%)
ASTHENIA	0	1 (<1%)
AXILLARY PAIN	1 (<1%)	0
CHEST PAIN	3 (<1%)	0
CHILLS	3 (<1%)	1 (<1%)
FATIGUE	3 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
FEELING HOT	1 (<1%)	0
INDURATION	1 (<1%)	1 (<1%)
INFLUENZA LIKE ILLNESS	5 (<1%)	1 (<1%)
INJECTION SITE BRUISING	1 (<1%)	0
INJECTION SITE ERYTHEMA	12 (1%)	0
INJECTION SITE HAEMORRHAGE	1 (<1%)	0
INJECTION SITE INDURATION	6 (1%)	1 (<1%)
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	9 (1%)	1 (<1%)
INJECTION SITE PRURITUS	4 (<1%)	3 (1%)
INJECTION SITE SWELLING	1 (<1%)	0
INJECTION SITE WARMTH	2 (<1%)	0
MALAISE	16 (1%)	3 (1%)
OEDEMA PERIPHERAL	1 (<1%)	0
PYREXIA	1 (<1%)	0
THIRST	1 (<1%)	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0
BILIARY COLIC	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
IMMUNE SYSTEM DISORDERS		
DRUG HYPERSENSITIVITY	0	1 (<1%)
INFECTIONS & INFESTATIONS	61 (5%)	32 (6%)
ABSCESS LIMB	1 (<1%)	0
ACUTE SINUSITIS	1 (<1%)	1 (<1%)
ACUTE TONSILLITIS	1 (<1%)	0
BREAST CELLULITIS	0	1 (<1%)
BRONCHITIS	1 (<1%)	1 (<1%)
BRONCHOPNEUMONIA	1 (<1%)	0
CELLULITIS	1 (<1%)	0
CONJUNCTIVITIS BACTERIAL	0	1 (<1%)
EAR INFECTION	2 (<1%)	0
FUNGAL INFECTION	1 (<1%)	0
GASTROENTERITIS	3 (<1%)	3 (1%)
HORDEOLUM	1 (<1%)	0
INFECTION PARASITIC	0	1 (<1%)
INFLUENZA	2 (<1%)	1 (<1%)
NASOPHARYNGITIS	17 (1%)	6 (1%)
OMPHALITIS	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
INFECTIONS & INFESTATIONS		
ORAL HERPES	2 (<1%)	2 (<1%)
OTITIS MEDIA	1 (<1%)	1 (<1%)
PELVIC INFLAMMATORY DISEASE	2 (<1%)	0
PERTUSSIS	1 (<1%)	0
PHARYNGITIS	3 (<1%)	4 (1%)
PHARYNGITIS STREPTOCOCCAL	0	1 (<1%)
POSTOPERATIVE WOUND INFECTION	0	1 (<1%)
RHINITIS	2 (<1%)	2 (<1%)
SINUSITIS	4 (<1%)	1 (<1%)
SYPHILIS	0	1 (<1%)
TINEA CRURIS	0	1 (<1%)
TONSILLITIS	1 (<1%)	0
TOOTH ABSCESS	1 (<1%)	0
UPPER RESPIRATORY TRACT INFECTION	4 (<1%)	3 (1%)
URINARY TRACT INFECTION	1 (<1%)	3 (1%)
VAGINAL INFECTION	1 (<1%)	0
VIRAL INFECTION	3 (<1%)	0
VIRAL PHARYNGITIS	3 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
INJURY & POISONING	5 (<1%)	5 (1%)
ACCIDENTAL NEEDLE STICK	1 (<1%)	0
FALL	0	1 (<1%)
INJURY	2 (<1%)	1 (<1%)
JOINT SPRAIN	0	1 (<1%)
MUSCLE STRAIN	1 (<1%)	0
SKIN LACERATION	0	1 (<1%)
SUNBURN	0	1 (<1%)
WOUND	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
INCREASED APPETITE	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	22 (2%)	16 (3%)
ARTHRALGIA	7 (1%)	2 (<1%)
BACK PAIN	6 (1%)	4 (1%)
MUSCLE SPASMS	1 (<1%)	5 (1%)
MUSCULAR WEAKNESS	1 (<1%)	0
MUSCULOSKELETAL CHEST PAIN	0	1 (<1%)
MYALGIA	8 (1%)	4 (1%)
NECK PAIN	2 (<1%)	1 (<1%)
PAIN IN EXTREMITY	2 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
NERVOUS SYSTEM DISORDERS	48 (4%)	18 (3%)
DIZZINESS	8 (1%)	4 (1%)
HEADACHE	29 (3%)	12 (2%)
MIGRAINE	6 (1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	1 (<1%)	0
PARAESTHESIA	2 (<1%)	2 (<1%)
SINUS HEADACHE	1 (<1%)	0
SOMNOLENCE	3 (<1%)	0
SYNCOPE VASOVAGAL	2 (<1%)	0
PSYCHIATRIC DISORDERS	4 (<1%)	4 (1%)
ANXIETY	1 (<1%)	1 (<1%)
DEPRESSION	1 (<1%)	3 (1%)
INSOMNIA	2 (<1%)	0
RENAL & URINARY DISORDERS	1 (<1%)	0
NEPHROLITHIASIS	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	13 (1%)	5 (1%)
DYSMENORRHOEA	13 (1%)	3 (1%)
VAGINAL DISCHARGE	0	1 (<1%)
VULVOVAGINAL BURNING SENSATION	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
RESP., THORACIC & MEDIASTINAL DIS.	14 (1%)	7 (1%)
BRONCHIAL HYPERREACTIVITY	1 (<1%)	0
COUGH	3 (<1%)	0
DYSPHONIA	1 (<1%)	0
DYSPNOEA	2 (<1%)	1 (<1%)
NASAL CONGESTION	2 (<1%)	0
PHARYNGOLARYNGEAL PAIN	7 (1%)	3 (1%)
PULMONARY CONGESTION	0	2 (<1%)
RHINITIS ALLERGIC	1 (<1%)	1 (<1%)
RHINORRHOEA	1 (<1%)	0
SINUS CONGESTION	1 (<1%)	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	8 (1%)	9 (2%)
ANGIOEDEMA	0	1 (<1%)
DERMAL CYST	1 (<1%)	0
DERMATITIS ATOPIC	0	1 (<1%)
DERMATITIS CONTACT	0	1 (<1%)
ECCHYMOSIS	1 (<1%)	0
ERYTHEMA	1 (<1%)	2 (<1%)
HYPERHIDROSIS	0	1 (<1%)
INGROWING NAIL	0	1 (<1%)
PRURITUS	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.2

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
RASH	4 (<1%)	0
RASH MACULAR	0	1 (<1%)
URTICARIA	0	1 (<1%)
VASCULAR DISORDERS	1 (<1%)	2 (<1%)
HYPERTENSION	1 (<1%)	1 (<1%)
HYPOTENSION	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	285 (20%)	146 (22%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	9 (1%)	1 (<1%)
LYMPHADENOPATHY	9 (1%)	1 (<1%)
EAR & LABYRINTH DISORDERS	4 (<1%)	5 (1%)
EAR PAIN	1 (<1%)	2 (<1%)
TINNITUS	2 (<1%)	0
VERTIGO	1 (<1%)	3 (<1%)
EYE DISORDERS	5 (<1%)	3 (<1%)
BLEPHARITIS	1 (<1%)	0
CONJUNCTIVITIS	0	1 (<1%)
CONJUNCTIVITIS ALLERGIC	0	1 (<1%)
EYE DISCHARGE	1 (<1%)	0
EYE IRRITATION	1 (<1%)	0
EYE PAIN	0	1 (<1%)
EYE SWELLING	1 (<1%)	0
TRICHIASIS	1 (<1%)	0
GASTROINTESTINAL DISORDERS	38 (3%)	21 (3%)
ABDOMINAL DISTENSION	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GASTROINTESTINAL DISORDERS		
ABDOMINAL PAIN	4 (<1%)	4 (1%)
ABDOMINAL PAIN UPPER	2 (<1%)	1 (<1%)
APHTHOUS STOMATITIS	0	1 (<1%)
COLITIS	0	1 (<1%)
CONSTIPATION	1 (<1%)	1 (<1%)
DIARRHOEA	9 (1%)	4 (1%)
DRY MOUTH	1 (<1%)	0
DYSPEPSIA	6 (<1%)	2 (<1%)
FOOD POISONING	1 (<1%)	0
GASTRITIS	2 (<1%)	0
GASTROINTESTINAL INFLAMMATION	0	1 (<1%)
GASTROINTESTINAL PAIN	1 (<1%)	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (<1%)	0
GLOSSODYNIA	1 (<1%)	0
HAEMORRHOIDS	2 (<1%)	0
HYPERCHLORHYDRIA	1 (<1%)	0
MELAENA	1 (<1%)	0
NAUSEA	3 (<1%)	1 (<1%)
ODYNOPHAGIA	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GASTROINTESTINAL DISORDERS		
ORAL PAIN	1 (<1%)	0
STOMACH DISCOMFORT	1 (<1%)	0
STOMATITIS	1 (<1%)	0
TOOTHACHE	0	3 (<1%)
VOMITING	5 (<1%)	2 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	76 (5%)	25 (4%)
ASTHENIA	1 (<1%)	1 (<1%)
AXILLARY PAIN	2 (<1%)	0
CHEST PAIN	1 (<1%)	1 (<1%)
CHILLS	6 (<1%)	1 (<1%)
DISCOMFORT	1 (<1%)	0
FATIGUE	6 (<1%)	1 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)
INDURATION	5 (<1%)	0
INFLUENZA LIKE ILLNESS	5 (<1%)	2 (<1%)
INJECTION SITE BRUISING	0	1 (<1%)
INJECTION SITE ERYTHEMA	9 (1%)	1 (<1%)
INJECTION SITE HAEMORRHAGE	2 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
INJECTION SITE INDURATION	6 (<1%)	0
INJECTION SITE IRRITATION	1 (<1%)	0
INJECTION SITE MASS	1 (<1%)	0
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	13 (1%)	5 (1%)
INJECTION SITE PRURITUS	12 (1%)	1 (<1%)
INJECTION SITE REACTION	2 (<1%)	0
INJECTION SITE WARMTH	4 (<1%)	3 (<1%)
MALAISE	18 (1%)	4 (1%)
OEDEMA PERIPHERAL	1 (<1%)	0
PAIN	3 (<1%)	2 (<1%)
PYREXIA	2 (<1%)	0
TENDERNESS	1 (<1%)	0
THIRST	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	2 (<1%)	0
HYPERSENSITIVITY	1 (<1%)	0
MULTIPLE ALLERGIES	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
INFECTIONS & INFESTATIONS	79 (5%)	42 (6%)
ABSCESS ORAL	1 (<1%)	0
BACTERIAL INFECTION	1 (<1%)	0
BRONCHITIS	3 (<1%)	3 (<1%)
CYSTITIS	1 (<1%)	2 (<1%)
EAR INFECTION	2 (<1%)	0
FUNGAL INFECTION	0	3 (<1%)
FUNGAL SKIN INFECTION	0	2 (<1%)
GASTROENTERITIS	4 (<1%)	2 (<1%)
GASTROENTERITIS VIRAL	2 (<1%)	1 (<1%)
HELICOBACTER INFECTION	1 (<1%)	0
HERPES ZOSTER	0	1 (<1%)
INFLUENZA	1 (<1%)	1 (<1%)
INJECTION SITE INFECTION	1 (<1%)	0
LARYNGITIS	0	1 (<1%)
MASTITIS	1 (<1%)	0
NAIL BED INFECTION	0	1 (<1%)
NASOPHARYNGITIS	13 (1%)	6 (1%)
ONYCHOMYCOSIS	0	1 (<1%)
ORAL HERPES	2 (<1%)	3 (<1%)
OTITIS EXTERNA	0	1 (<1%)
OTITIS MEDIA	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
INFECTIONS & INFESTATIONS		
PHARYNGITIS	7 (<1%)	1 (<1%)
PHARYNGITIS BACTERIAL	0	1 (<1%)
PHARYNGITIS STREPTOCOCCAL	2 (<1%)	1 (<1%)
RESPIRATORY TRACT INFECTION	1 (<1%)	0
RHINITIS	9 (1%)	3 (<1%)
SINUSITIS	3 (<1%)	4 (1%)
TONSILLITIS	1 (<1%)	0
TOOTH ABSCESS	1 (<1%)	1 (<1%)
TOOTH INFECTION	3 (<1%)	2 (<1%)
UPPER RESPIRATORY TRACT INFECTION	3 (<1%)	2 (<1%)
URINARY TRACT INFECTION	7 (<1%)	3 (<1%)
VAGINAL INFECTION	1 (<1%)	0
VAGINITIS BACTERIAL	0	1 (<1%)
VIRAL INFECTION	6 (<1%)	1 (<1%)
VULVOVAGINAL MYCOTIC INFECTION	2 (<1%)	0
WOUND INFECTION	1 (<1%)	0
INJURY & POISONING	7 (<1%)	2 (<1%)
ANIMAL BITE	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
INJURY & POISONING		
CONTUSION	1 (<1%)	0
HEAD INJURY	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0
INJURY	0	1 (<1%)
JOINT SPRAIN	2 (<1%)	0
MULTIPLE INJURIES	0	1 (<1%)
PROCEDURAL PAIN	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
WOUND	1 (<1%)	0
INVESTIGATIONS	1 (<1%)	1 (<1%)
BLOOD POTASSIUM DECREASED	0	1 (<1%)
BLOOD PRESSURE INCREASED	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
INCREASED APPETITE	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	60 (4%)	35 (5%)
ARTHRALGIA	15 (1%)	11 (2%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
MUSCULO., CONNECT. TIS. & BONE DIS.		
BACK PAIN	16 (1%)	6 (1%)
COSTOCHONDRITIS	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)
JOINT HYPEREXTENSION	1 (<1%)	0
JOINT STIFFNESS	1 (<1%)	0
MEDIAL TIBIAL STRESS SYNDROME	1 (<1%)	0
MUSCLE CONTRACTURE	1 (<1%)	0
MUSCLE SPASMS	3 (<1%)	0
MUSCULOSKELETAL PAIN	2 (<1%)	2 (<1%)
MUSCULOSKELETAL STIFFNESS	1 (<1%)	2 (<1%)
MYALGIA	17 (1%)	6 (1%)
NECK PAIN	5 (<1%)	0
OSTEOCHONDROSIS	1 (<1%)	0
PAIN IN EXTREMITY	9 (1%)	10 (2%)
SPINAL DEFORMITY	1 (<1%)	0
TENDONITIS	1 (<1%)	0
TORTICOLLIS	0	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)		
POLYCYTHAEMIA VERA	1 (<1%)	0
UTERINE LEIOMYOMA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	50 (3%)	34 (5%)
BURNING SENSATION	1 (<1%)	1 (<1%)
CARPAL TUNNEL SYNDROME	0	2 (<1%)
DIZZINESS	6 (<1%)	9 (1%)
HEADACHE	31 (2%)	16 (2%)
MIGRAINE	3 (<1%)	0
NEURALGIA	0	1 (<1%)
PARAESTHESIA	4 (<1%)	2 (<1%)
SCIATICA	1 (<1%)	2 (<1%)
SINUS HEADACHE	6 (<1%)	1 (<1%)
SOMNOLENCE	2 (<1%)	2 (<1%)
SYNCOPE	1 (<1%)	0
PSYCHIATRIC DISORDERS	8 (1%)	1 (<1%)
ANXIETY	1 (<1%)	0
DEPRESSION	3 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
PSYCHIATRIC DISORDERS		
INSOMNIA	3 (<1%)	1 (<1%)
POST-TRAUMATIC STRESS DISORDER	1 (<1%)	0
RESTLESSNESS	1 (<1%)	0
RENAL & URINARY DISORDERS	2 (<1%)	0
CALCULUS URETERIC	1 (<1%)	0
NEPHROLITHIASIS	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	7 (<1%)	6 (1%)
BREAST PAIN	0	1 (<1%)
DYSMENORRHOEA	6 (<1%)	2 (<1%)
OLIGOMENORRHOEA	1 (<1%)	0
POSTMENOPAUSAL HAEMORRHAGE	0	1 (<1%)
PREMENSTRUAL SYNDROME	0	1 (<1%)
VAGINAL DISCHARGE	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	30 (2%)	8 (1%)
COUGH	4 (<1%)	3 (<1%)
DRY THROAT	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
RESP., THORACIC & MEDIASTINAL DIS.		
EPISTAXIS	3 (<1%)	1 (<1%)
NASAL CONGESTION	4 (<1%)	1 (<1%)
NASAL DRYNESS	1 (<1%)	0
PHARYNGOLARYNGEAL PAIN	12 (1%)	4 (1%)
RHINITIS ALLERGIC	4 (<1%)	1 (<1%)
RHINORRHOEA	2 (<1%)	1 (<1%)
SINUS CONGESTION	1 (<1%)	0
THROAT IRRITATION	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	20 (1%)	10 (2%)
ACNE	0	1 (<1%)
DERMATITIS ALLERGIC	1 (<1%)	0
DERMATITIS CONTACT	1 (<1%)	0
ECCHYMOSIS	0	1 (<1%)
ERYTHEMA	9 (1%)	1 (<1%)
HYPERHIDROSIS	2 (<1%)	2 (<1%)
PRURIGO	0	1 (<1%)
PRURITUS	1 (<1%)	0
PRURITUS GENERALISED	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 33.3

Summary of Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
RASH	6 (<1%)	4 (1%)
SKIN DISCOLOURATION	1 (<1%)	0
URTICARIA	2 (<1%)	0
VASCULAR DISORDERS	6 (<1%)	4 (1%)
FLUSHING	2 (<1%)	2 (<1%)
HYPERTENSION	4 (<1%)	1 (<1%)
HYPERTENSIVE CRISIS	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 34.1

Summary of Treatment-emergent Adverse Events Occurring Within 30 Minutes Post-vaccination, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	8 (<1%)	1 (<1%)	9 (<1%)	6 (1%)	0	2 (<1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
NAUSEA	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	0	1 (<1%)
FEELING HOT	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE BRUISING	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE ERYTHEMA	1 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)
INJECTION SITE INDURATION	0	1 (<1%)	1 (<1%)	0	0	0
INJECTION SITE PRURITUS	0	0	0	1 (<1%)	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
MUSCULAR WEAKNESS	1 (<1%)	0	1 (<1%)	0	0	0
PAIN IN EXTREMITY	0	1 (<1%)	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	2 (<1%)	0	2 (<1%)	4 (1%)	0	1 (<1%)
DIZZINESS	0	0	0	1 (<1%)	0	0
HEADACHE	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
SYNCOPE	1 (<1%)	0	1 (<1%)	2 (<1%)	0	0
SYNCOPE VASOVAGAL	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 34.1

Summary of Treatment-emergent Adverse Events Occurring Within 30 Minutes Post-vaccination, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
SKIN & SUBCUTANEOUS TIS. DISORDERS	2 (<1%)	0	2 (<1%)	0	0	0
ERYTHEMA	1 (<1%)	0	1 (<1%)	0	0	0
HYPOAESTHESIA FACIAL	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 34.2

Summary of Treatment-emergent Adverse Events Occurring Within 30 Minutes Post-vaccination, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	11 (1%)	4 (1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0
VERTIGO	1 (<1%)	0
GASTROINTESTINAL DISORDERS	2 (<1%)	0
NAUSEA	2 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	2 (<1%)
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	2 (<1%)	1 (<1%)
INJECTION SITE PRURITUS	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	5 (<1%)	1 (<1%)
DIZZINESS	2 (<1%)	0
HEADACHE	2 (<1%)	0
PARAESTHESIA	0	1 (<1%)
SYNCOPE VASOVAGAL	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	1 (<1%)	0
COUGH	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 34.2

Summary of Treatment-emergent Adverse Events Occurring Within 30 Minutes Post-vaccination, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	1 (<1%)
ECCHYMOSIS	1 (<1%)	0
ERYTHEMA	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 34.3

Summary of Treatment-emergent Adverse Events Occurring Within 30 Minutes Post-vaccination, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	6 (<1%)	3 (<1%)
GASTROINTESTINAL DISORDERS	2 (<1%)	0
NAUSEA	1 (<1%)	0
STOMACH DISCOMFORT	1 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	4 (<1%)	2 (<1%)
INDURATION	1 (<1%)	0
INJECTION SITE BRUISING	0	1 (<1%)
INJECTION SITE HAEMORRHAGE	0	1 (<1%)
INJECTION SITE PAIN	2 (<1%)	0
INJECTION SITE PRURITUS	1 (<1%)	0
MALAISE	2 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0
ARTHRALGIA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	0
HEADACHE	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0
RASH	1 (<1%)	0
VASCULAR DISORDERS	0	1 (<1%)
FLUSHING	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_30M_35_55.SAS(WARTERO) 10JUL08, 08:25 SAS.9.1 - AESUM_TRT_30M_35_55

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)
ANY ADVERSE EVENT	269 (11%)	76 (7%)	115 (8%)	460 (9%)	134 (8%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	2 (<1%)	0	2 (<1%)	4 (<1%)	2 (<1%)
ANAEMIA	1 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)
DEFICIENCY ANAEMIA	0	0	0	0	1 (<1%)
SPLENOMEGALY	1 (<1%)	0	0	1 (<1%)	0
CARDIAC DISORDERS	3 (<1%)	0	1 (<1%)	4 (<1%)	4 (<1%)
EXTRASYSTOLES	0	0	0	0	1 (<1%)
MITRAL VALVE PROLAPSE	1 (<1%)	0	0	1 (<1%)	0
PALPITATIONS	1 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME	1 (<1%)	0	0	1 (<1%)	0
TACHYCARDIA	0	0	0	0	3 (<1%)
EAR & LABYRINTH DISORDERS	3 (<1%)	1 (<1%)	1 (<1%)	5 (<1%)	0
EAR PAIN	1 (<1%)	0	0	1 (<1%)	0
EUSTACHIAN TUBE DYSFUNCTION	1 (<1%)	0	0	1 (<1%)	0
HYPOACUSIS	0	0	1 (<1%)	1 (<1%)	0
VERTIGO	1 (<1%)	1 (<1%)	0	2 (<1%)	0
ENDOCRINE DISORDERS	0	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)
HYPOTHYROIDISM	0	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
EYE DISORDERS	1 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)
BLEPHARITIS	0	0	1 (<1%)	1 (<1%)	0
PTERYGIUM	0	0	0	0	1 (<1%)
RETINAL DETACHMENT	0	0	1 (<1%)	1 (<1%)	0
ULCERATIVE KERATITIS	1 (<1%)	0	0	1 (<1%)	0
GASTROINTESTINAL DISORDERS	26 (1%)	15 (1%)	11 (1%)	52 (1%)	10 (1%)
ABDOMINAL DISCOMFORT	1 (<1%)	0	1 (<1%)	2 (<1%)	0
ABDOMINAL DISTENSION	0	0	1 (<1%)	1 (<1%)	0
ABDOMINAL HERNIA	0	1 (<1%)	0	1 (<1%)	0
ABDOMINAL PAIN	4 (<1%)	2 (<1%)	0	6 (<1%)	4 (<1%)
ABDOMINAL PAIN UPPER	1 (<1%)	0	0	1 (<1%)	0
ANAL FISSURE	1 (<1%)	0	0	1 (<1%)	0
APHTHOUS STOMATITIS	1 (<1%)	0	0	1 (<1%)	0
CONSTIPATION	2 (<1%)	0	0	2 (<1%)	0
DIARRHOEA	7 (<1%)	1 (<1%)	0	8 (<1%)	0
DIVERTICULUM INTESTINAL	0	0	1 (<1%)	1 (<1%)	0
GASTRIC ULCER	0	0	1 (<1%)	1 (<1%)	0
GASTRITIS	0	5 (<1%)	5 (<1%)	10 (<1%)	3 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	0
IRRITABLE BOWEL SYNDROME	1 (<1%)	3 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
MALLORY-WEISS SYNDROME	0	1 (<1%)	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
GASTROINTESTINAL DISORDERS					
NAUSEA	1 (<1%)	1 (<1%)	0	2 (<1%)	0
ORAL DISORDER	0	0	0	0	1 (<1%)
STOMATITIS	1 (<1%)	0	0	1 (<1%)	0
TOOTHACHE	2 (<1%)	1 (<1%)	0	3 (<1%)	1 (<1%)
VOMITING	5 (<1%)	0	0	5 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	13 (1%)	2 (<1%)	6 (<1%)	21 (<1%)	5 (<1%)
CHEST PAIN	1 (<1%)	0	2 (<1%)	3 (<1%)	2 (<1%)
FATIGUE	0	0	2 (<1%)	2 (<1%)	1 (<1%)
GAIT DISTURBANCE	1 (<1%)	0	0	1 (<1%)	0
GENERALISED OEDEMA	0	0	0	0	1 (<1%)
HERNIA	0	0	1 (<1%)	1 (<1%)	0
INFLUENZA LIKE ILLNESS	0	1 (<1%)	0	1 (<1%)	0
MALAISE	0	1 (<1%)	1 (<1%)	2 (<1%)	0
OEDEMA PERIPHERAL	1 (<1%)	0	0	1 (<1%)	0
PYREXIA	10 (<1%)	0	0	10 (<1%)	1 (<1%)
HEPATO-BILIARY DISORDERS	0	0	1 (<1%)	1 (<1%)	0
GALLBLADDER POLYP	0	0	1 (<1%)	1 (<1%)	0
HEPATOMEGALY	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
IMMUNE SYSTEM DISORDERS	4 (<1%)	2 (<1%)	0	6 (<1%)	1 (<1%)
ALLERGIC OEDEMA	1 (<1%)	0	0	1 (<1%)	0
DRUG HYPERSENSITIVITY	0	1 (<1%)	0	1 (<1%)	1 (<1%)
HYPERSENSITIVITY	1 (<1%)	1 (<1%)	0	2 (<1%)	0
SEASONAL ALLERGY	2 (<1%)	0	0	2 (<1%)	0
INFECTIONS & INFESTATIONS	94 (4%)	22 (2%)	24 (2%)	140 (3%)	19 (1%)
ABSCESS LIMB	1 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
APPENDICITIS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
BRONCHITIS	6 (<1%)	5 (<1%)	4 (<1%)	15 (<1%)	1 (<1%)
BRONCHOPNEUMONIA	1 (<1%)	0	0	1 (<1%)	0
CANDIDIASIS	1 (<1%)	0	0	1 (<1%)	0
CELLULITIS	3 (<1%)	2 (<1%)	3 (<1%)	8 (<1%)	3 (<1%)
CONJUNCTIVITIS BACTERIAL	0	0	1 (<1%)	1 (<1%)	0
CYSTITIS	0	0	1 (<1%)	1 (<1%)	0
EAR INFECTION	3 (<1%)	0	0	3 (<1%)	0
ERYTHEMA INFECTIOSUM	2 (<1%)	0	0	2 (<1%)	0
EXTERNAL EAR CELLULITIS	1 (<1%)	0	0	1 (<1%)	0
EYE INFECTION TOXOPLASMAL	0	0	0	0	1 (<1%)
FOLLICULITIS	0	0	0	0	1 (<1%)
FUNGAL INFECTION	0	1 (<1%)	0	1 (<1%)	0
GASTROENTERITIS	5 (<1%)	0	0	5 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
GASTROENTERITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0
GENITAL HERPES	0	0	0	0	1 (<1%)
HELICOBACTER GASTRITIS	0	2 (<1%)	0	2 (<1%)	0
HERPES ZOSTER	2 (<1%)	0	2 (<1%)	4 (<1%)	1 (<1%)
HIV INFECTION	0	0	0	0	1 (<1%)
IMPETIGO	1 (<1%)	0	0	1 (<1%)	0
INFECTIOUS MONONUCLEOSIS	2 (<1%)	0	0	2 (<1%)	0
INFLUENZA	17 (1%)	0	0	17 (<1%)	0
KIDNEY INFECTION	0	0	1 (<1%)	1 (<1%)	0
LARYNGITIS	1 (<1%)	0	0	1 (<1%)	0
LOCALISED INFECTION	0	0	0	0	2 (<1%)
MENINGITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0
MYCOPLASMA INFECTION	1 (<1%)	0	0	1 (<1%)	0
NAIL BED INFECTION	1 (<1%)	0	0	1 (<1%)	0
NASOPHARYNGITIS	7 (<1%)	0	0	7 (<1%)	0
ORAL HERPES	1 (<1%)	0	0	1 (<1%)	0
OTITIS MEDIA	1 (<1%)	0	0	1 (<1%)	0
PARASITIC GASTROENTERITIS	0	1 (<1%)	0	1 (<1%)	0
PARONYCHIA	2 (<1%)	0	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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(Study V59P18 excluded)

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...Continued from previous page					
INFECTIONS & INFESTATIONS					
PERIORBITAL CELLULITIS	0	0	1 (<1%)	1 (<1%)	0
PERITONSILLAR ABSCESS	2 (<1%)	0	0	2 (<1%)	0
PHARYNGITIS	18 (1%)	1 (<1%)	1 (<1%)	20 (<1%)	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	0	1 (<1%)	0
PILONIDAL CYST	0	0	0	0	1 (<1%)
PNEUMONIA	3 (<1%)	4 (<1%)	5 (<1%)	12 (<1%)	0
RHINITIS	0	1 (<1%)	0	1 (<1%)	0
SIALOADENITIS	1 (<1%)	0	0	1 (<1%)	0
SINUSITIS	4 (<1%)	0	1 (<1%)	5 (<1%)	0
STAPHYLOCOCCAL INFECTION	3 (<1%)	0	0	3 (<1%)	1 (<1%)
SUBCUTANEOUS ABSCESS	0	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
TINEA VERSICOLOUR	2 (<1%)	0	0	2 (<1%)	0
TONSILLITIS	6 (<1%)	0	0	6 (<1%)	1 (<1%)
TOOTH ABSCESS	0	0	1 (<1%)	1 (<1%)	0
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	0	1 (<1%)	0
URINARY TRACT INFECTION	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
VAGINAL INFECTION	0	0	0	0	1 (<1%)
VAGINITIS BACTERIAL	0	1 (<1%)	0	1 (<1%)	0
VARICELLA	3 (<1%)	1 (<1%)	0	4 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
VIRAL INFECTION	2 (<1%)	0	0	2 (<1%)	0
VIRAL PHARYNGITIS	0	0	0	0	1 (<1%)
VIRAL RASH	1 (<1%)	0	0	1 (<1%)	0
VULVOVAGINITIS TRICHOMONAL	0	0	1 (<1%)	1 (<1%)	1 (<1%)
INJURY & POISONING	63 (3%)	13 (1%)	14 (1%)	90 (2%)	31 (2%)
ACCIDENTAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
ANIMAL BITE	0	0	1 (<1%)	1 (<1%)	0
ANKLE FRACTURE	0	0	0	0	1 (<1%)
ARTHROPOD STING	0	1 (<1%)	0	1 (<1%)	1 (<1%)
BACK INJURY	1 (<1%)	0	0	1 (<1%)	1 (<1%)
BURNS SECOND DEGREE	0	0	0	0	1 (<1%)
CHEST INJURY	1 (<1%)	0	0	1 (<1%)	0
CLAVICLE FRACTURE	3 (<1%)	0	1 (<1%)	4 (<1%)	0
CONCUSSION	4 (<1%)	0	0	4 (<1%)	0
CONTUSION	8 (<1%)	1 (<1%)	0	9 (<1%)	1 (<1%)
DISLOCATION OF STERNUM	0	0	0	0	1 (<1%)
EPICONDYLITIS	1 (<1%)	0	0	1 (<1%)	0
EXCORIATION	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
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INJURY & POISONING					
FACIAL BONES FRACTURE	0	0	0	0	1 (<1%)
FALL	0	0	1 (<1%)	1 (<1%)	1 (<1%)
FEMUR FRACTURE	1 (<1%)	0	0	1 (<1%)	0
FOOT FRACTURE	6 (<1%)	1 (<1%)	0	7 (<1%)	1 (<1%)
FRACTURED COCCYX	0	1 (<1%)	0	1 (<1%)	0
GUN SHOT WOUND	0	0	0	0	1 (<1%)
HAND FRACTURE	5 (<1%)	0	0	5 (<1%)	1 (<1%)
HEAD INJURY	2 (<1%)	0	1 (<1%)	3 (<1%)	1 (<1%)
HEAT STROKE	1 (<1%)	0	0	1 (<1%)	0
INJURY	2 (<1%)	1 (<1%)	7 (<1%)	10 (<1%)	2 (<1%)
INTENTIONAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
JAW FRACTURE	1 (<1%)	0	0	1 (<1%)	0
JOINT DISLOCATION	3 (<1%)	1 (<1%)	0	4 (<1%)	1 (<1%)
JOINT INJURY	3 (<1%)	0	1 (<1%)	4 (<1%)	1 (<1%)
JOINT SPRAIN	5 (<1%)	3 (<1%)	0	8 (<1%)	3 (<1%)
LACERATION	1 (<1%)	1 (<1%)	0	2 (<1%)	0
LIGAMENT RUPTURE	2 (<1%)	0	0	2 (<1%)	0
LIMB INJURY	6 (<1%)	0	0	6 (<1%)	1 (<1%)
MENISCUS LESION	0	0	0	0	2 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INJURY & POISONING					
MUSCLE STRAIN	2 (<1%)	0	0	2 (<1%)	0
OVERDOSE	0	1 (<1%)	0	1 (<1%)	0
PELVIC FRACTURE	1 (<1%)	0	0	1 (<1%)	0
PROCEDURAL PAIN	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RADIUS FRACTURE	1 (<1%)	0	1 (<1%)	2 (<1%)	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	1 (<1%)	0	3 (<1%)	0
SKIN LACERATION	2 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)
SOFT TISSUE INJURY	0	1 (<1%)	0	1 (<1%)	0
SPINAL COMPRESSION FRACTURE	0	0	0	0	1 (<1%)
THERAPEUTIC AGENT TOXICITY	0	0	0	0	1 (<1%)
TRAUMATIC BRAIN INJURY	1 (<1%)	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	1 (<1%)	1 (<1%)
WOUND	1 (<1%)	0	0	1 (<1%)	1 (<1%)
WRIST FRACTURE	1 (<1%)	0	0	1 (<1%)	2 (<1%)
INVESTIGATIONS	2 (<1%)	0	4 (<1%)	6 (<1%)	2 (<1%)
BLOOD CHOLESTEROL INCREASED	0	0	0	0	1 (<1%)
CARDIAC MURMUR	0	0	0	0	1 (<1%)
ENDOSCOPY	0	0	1 (<1%)	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INVESTIGATIONS					
HEART RATE INCREASED	1 (<1%)	0	0	1 (<1%)	0
LIVER FUNCTION TEST ABNORMAL	0	0	1 (<1%)	1 (<1%)	0
TRANSAMINASES INCREASED	0	0	1 (<1%)	1 (<1%)	0
WEIGHT DECREASED	0	0	1 (<1%)	1 (<1%)	0
WEIGHT INCREASED	1 (<1%)	0	0	1 (<1%)	1 (<1%)
METABOLISM & NUTRITION DISORDERS	4 (<1%)	0	8 (1%)	12 (<1%)	2 (<1%)
DEHYDRATION	2 (<1%)	0	0	2 (<1%)	0
DYSLIPIDAEMIA	0	0	4 (<1%)	4 (<1%)	0
HYPERCHOLESTEROLAEMIA	0	0	2 (<1%)	2 (<1%)	1 (<1%)
HYPERINSULINISM	1 (<1%)	0	0	1 (<1%)	0
HYPERLIPIDAEMIA	1 (<1%)	0	2 (<1%)	3 (<1%)	0
HYPOKALAEMIA	0	0	0	0	1 (<1%)
METABOLIC SYNDROME	1 (<1%)	0	0	1 (<1%)	0
TYPE 2 DIABETES MELLITUS	0	0	1 (<1%)	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	24 (1%)	4 (<1%)	18 (1%)	46 (1%)	20 (1%)
ARTHRALGIA	8 (<1%)	0	1 (<1%)	9 (<1%)	4 (<1%)
ARTHRITIS	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
MUSCULO., CONNECT. TIS. & BONE DIS.					
BACK PAIN	3 (<1%)	2 (<1%)	2 (<1%)	7 (<1%)	7 (<1%)
COSTOCHONDRITIS	0	0	1 (<1%)	1 (<1%)	0
ENTHESOPATHY	1 (<1%)	0	0	1 (<1%)	0
EPIPHYSIOLYSIS	1 (<1%)	0	0	1 (<1%)	0
EXOSTOSIS	0	0	1 (<1%)	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	2 (<1%)	2 (<1%)	2 (<1%)
JOINT SWELLING	0	0	1 (<1%)	1 (<1%)	1 (<1%)
LUMBAR SPINE FLATTENING	1 (<1%)	0	0	1 (<1%)	0
MUSCLE SPASMS	0	2 (<1%)	0	2 (<1%)	1 (<1%)
MUSCULOSKELETAL CHEST PAIN	1 (<1%)	0	0	1 (<1%)	0
MUSCULOSKELETAL DISORDER	1 (<1%)	0	0	1 (<1%)	0
MUSCULOSKELETAL PAIN	2 (<1%)	0	3 (<1%)	5 (<1%)	1 (<1%)
MYALGIA	1 (<1%)	0	1 (<1%)	2 (<1%)	0
NECK PAIN	1 (<1%)	0	0	1 (<1%)	1 (<1%)
OSTEOARTHRITIS	0	0	1 (<1%)	1 (<1%)	2 (<1%)
OSTEOCHONDROSIS	2 (<1%)	0	0	2 (<1%)	0
PAIN IN EXTREMITY	4 (<1%)	0	1 (<1%)	5 (<1%)	1 (<1%)
PLANTAR FASCIITIS	0	0	1 (<1%)	1 (<1%)	0
ROTATOR CUFF SYNDROME	2 (<1%)	0	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

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Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
MUSCULO., CONNECT. TIS. & BONE DIS.					
SYNOVIAL CYST	0	0	1 (<1%)	1 (<1%)	0
TEMPOROMANDIBULAR JOINT SYNDROME	0	0	1 (<1%)	1 (<1%)	0
TENDONITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	1 (<1%)	4 (<1%)	6 (<1%)	2 (<1%)
ACROCHORDON	0	0	1 (<1%)	1 (<1%)	0
BREAST NEOPLASM	0	0	0	0	1 (<1%)
MELANOCYTIC NAEVUS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
MORTON'S NEUROMA	0	0	1 (<1%)	1 (<1%)	0
PAPILLOMA	0	0	1 (<1%)	1 (<1%)	0
UTERINE LEIOMYOMA	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
NERVOUS SYSTEM DISORDERS	28 (1%)	8 (1%)	7 (<1%)	43 (1%)	16 (1%)
CARPAL TUNNEL SYNDROME	1 (<1%)	0	1 (<1%)	2 (<1%)	0
CONVULSION	1 (<1%)	0	0	1 (<1%)	0
DIZZINESS	4 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
DYSTONIA	0	1 (<1%)	0	1 (<1%)	0
EPILEPSY	0	0	1 (<1%)	1 (<1%)	0
FACIAL PALSY	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
NERVOUS SYSTEM DISORDERS					
GRAND MAL CONVULSION	0	1 (<1%)	0	1 (<1%)	0
HEADACHE	12 (<1%)	2 (<1%)	0	14 (<1%)	5 (<1%)
HYPOAESTHESIA	1 (<1%)	0	0	1 (<1%)	0
MIGRAINE	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	5 (<1%)
MYASTHENIA GRAVIS	1 (<1%)	0	0	1 (<1%)	0
MYOCLONIC EPILEPSY	1 (<1%)	0	0	1 (<1%)	0
PARAESTHESIA	0	1 (<1%)	0	1 (<1%)	0
PETIT MAL EPILEPSY	0	1 (<1%)	0	1 (<1%)	0
POST HERPETIC NEURALGIA	0	0	0	0	1 (<1%)
SOMNOLENCE	0	0	0	0	1 (<1%)
SYNCOPE	4 (<1%)	0	2 (<1%)	6 (<1%)	0
SYNCOPE VASOVAGAL	1 (<1%)	0	0	1 (<1%)	2 (<1%)
TENSION HEADACHE	1 (<1%)	0	2 (<1%)	3 (<1%)	0
TREMOR	1 (<1%)	0	0	1 (<1%)	2 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	0	4 (<1%)	0	4 (<1%)	0
ABORTION SPONTANEOUS	0	3 (<1%)	0	3 (<1%)	0
ABORTION THREATENED	0	1 (<1%)	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)
PSYCHIATRIC DISORDERS	16 (1%)	4 (<1%)	5 (<1%)	25 (<1%)	8 (<1%)
ALCOHOL ABUSE	1 (<1%)	0	0	1 (<1%)	0
ANXIETY	4 (<1%)	3 (<1%)	2 (<1%)	9 (<1%)	1 (<1%)
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	4 (<1%)	0	0	4 (<1%)	3 (<1%)
CONVERSION DISORDER	0	1 (<1%)	0	1 (<1%)	0
DEPRESSION	6 (<1%)	0	2 (<1%)	8 (<1%)	2 (<1%)
MAJOR DEPRESSION	0	0	0	0	1 (<1%)
MENOPAUSAL DEPRESSION	0	0	1 (<1%)	1 (<1%)	0
SUICIDAL IDEATION	0	0	0	0	1 (<1%)
SUICIDE ATTEMPT	1 (<1%)	1 (<1%)	0	2 (<1%)	0
TIC	0	0	0	0	1 (<1%)
RENAL & URINARY DISORDERS	0	0	2 (<1%)	2 (<1%)	3 (<1%)
HAEMATURIA	0	0	1 (<1%)	1 (<1%)	0
NEPHROLITHIASIS	0	0	1 (<1%)	1 (<1%)	2 (<1%)
RENAL COLIC	0	0	0	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	5 (<1%)	3 (<1%)	5 (<1%)	13 (<1%)	5 (<1%)
BREAST MASS	0	0	1 (<1%)	1 (<1%)	0
BREAST PAIN	0	0	1 (<1%)	1 (<1%)	1 (<1%)
DYSMENORRHOEA	3 (<1%)	0	0	3 (<1%)	1 (<1%)
ERECTILE DYSFUNCTION	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
REPRODUCT. SYS. & BREAST DISORDERS					
FIBROCYSTIC BREAST DISEASE	1 (<1%)	0	0	1 (<1%)	0
MENOPAUSAL SYMPTOMS	0	0	1 (<1%)	1 (<1%)	0
MENORRHAGIA	0	0	0	0	1 (<1%)
OVARIAN CYST	0	1 (<1%)	2 (<1%)	3 (<1%)	0
TESTICULAR TORSION	1 (<1%)	0	0	1 (<1%)	0
VAGINAL DISCHARGE	0	1 (<1%)	0	1 (<1%)	1 (<1%)
VAGINAL HAEMORRHAGE	0	1 (<1%)	0	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	22 (1%)	8 (1%)	6 (<1%)	36 (1%)	8 (<1%)
ASTHMA	1 (<1%)	3 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
ASTHMA EXERCISE INDUCED	2 (<1%)	0	0	2 (<1%)	0
ASTHMATIC CRISIS	0	1 (<1%)	1 (<1%)	2 (<1%)	0
BRONCHIAL HYPERREACTIVITY	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
BRONCHOSPASM	2 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0	0	1 (<1%)
COUGH	1 (<1%)	0	0	1 (<1%)	1 (<1%)
DYSPNOEA	2 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)	0
EPISTAXIS	1 (<1%)	0	0	1 (<1%)	0
HYPERVENTILATION	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
RESP., THORACIC & MEDIASTINAL DIS.					
LARYNGITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)	0
PARANASAL SINUS HYPERSECRETION	0	0	0	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	2 (<1%)	0	0	2 (<1%)	0
PULMONARY EMBOLISM	0	1 (<1%)	0	1 (<1%)	0
RESPIRATORY FAILURE	0	1 (<1%)	0	1 (<1%)	0
RHINITIS ALLERGIC	7 (<1%)	0	1 (<1%)	8 (<1%)	4 (<1%)
RHINITIS SEASONAL	1 (<1%)	0	0	1 (<1%)	0
SNORING	1 (<1%)	0	0	1 (<1%)	0
WHEEZING	1 (<1%)	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	10 (<1%)	3 (<1%)	2 (<1%)	15 (<1%)	8 (<1%)
ACNE	0	1 (<1%)	0	1 (<1%)	1 (<1%)
ALOPECIA	0	0	0	0	1 (<1%)
ANGIOEDEMA	0	0	0	0	1 (<1%)
DERMATITIS	0	0	1 (<1%)	1 (<1%)	0
DERMATITIS ALLERGIC	0	1 (<1%)	0	1 (<1%)	1 (<1%)
DERMATITIS ATOPIC	1 (<1%)	0	0	1 (<1%)	0
DERMATITIS CONTACT	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
HYPERHIDROSIS	2 (<1%)	0	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
SKIN & SUBCUTANEOUS TIS. DISORDERS					
INGROWING NAIL	1 (<1%)	0	0	1 (<1%)	0
PANNICULITIS	0	0	0	0	1 (<1%)
PSORIASIS	0	0	1 (<1%)	1 (<1%)	0
RASH	0	0	0	0	1 (<1%)
SKIN NODULE	1 (<1%)	0	0	1 (<1%)	0
URTICARIA	4 (<1%)	0	0	4 (<1%)	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	3 (<1%)	2 (<1%)	2 (<1%)	7 (<1%)	3 (<1%)
CYST REMOVAL	1 (<1%)	0	0	1 (<1%)	0
HYSTERECTOMY	0	1 (<1%)	1 (<1%)	2 (<1%)	0
LIPOSUCTION	0	0	0	0	1 (<1%)
NEPHRECTOMY	0	1 (<1%)	0	1 (<1%)	0
PERIODONTAL OPERATION	1 (<1%)	0	0	1 (<1%)	0
ROTATOR CUFF REPAIR	0	0	1 (<1%)	1 (<1%)	0
SEPTOPLASTY	0	0	0	0	1 (<1%)
UMBILICAL HERNIA REPAIR	0	0	0	0	1 (<1%)
WISDOM TEETH REMOVAL	1 (<1%)	0	0	1 (<1%)	0
VASCULAR DISORDERS	0	0	7 (<1%)	7 (<1%)	5 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 35

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)
...Continued from previous page					
VASCULAR DISORDERS					
CIRCULATORY COLLAPSE	0	0	0	0	1 (<1%)
DEEP VEIN THROMBOSIS	0	0	1 (<1%)	1 (<1%)	0
HOT FLUSH	0	0	1 (<1%)	1 (<1%)	0
HYPERTENSION	0	0	4 (<1%)	4 (<1%)	2 (<1%)
HYPERTENSIVE CRISIS	0	0	1 (<1%)	1 (<1%)	1 (<1%)
PHLEBITIS	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - AESUM_ACWY_M26

Table 36.1

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
ANY ADVERSE EVENT	227 (11%)	42 (12%)	269 (11%)	48 (9%)	31 (15%)	36 (10%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)
ANAEMIA	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
SPLENOMEGALY	1 (<1%)	0	1 (<1%)	0	0	0
CARDIAC DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
MITRAL VALVE PROLAPSE	1 (<1%)	0	1 (<1%)	0	0	0
PALPITATIONS	1 (<1%)	0	1 (<1%)	0	0	0
POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME	1 (<1%)	0	1 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
EAR PAIN	1 (<1%)	0	1 (<1%)	0	0	0
EUSTACHIAN TUBE DYSFUNCTION	1 (<1%)	0	1 (<1%)	0	0	0
VERTIGO	1 (<1%)	0	1 (<1%)	0	0	0
EYE DISORDERS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
CONJUNCTIVITIS	0	0	0	0	1 (<1%)	0
ULCERATIVE KERATITIS	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	20 (1%)	6 (2%)	26 (1%)	1 (<1%)	4 (2%)	6 (2%)
ABDOMINAL DISCOMFORT	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - AESUM_TRT_M26_11_18

Table 36.1

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
...Continued from previous page						
GASTROINTESTINAL DISORDERS						
ABDOMINAL PAIN	3 (<1%)	1 (<1%)	4 (<1%)	0	2 (1%)	1 (<1%)
ABDOMINAL PAIN LOWER	0	0	0	0	1 (<1%)	0
ABDOMINAL PAIN UPPER	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)
ANAL FISSURE	1 (<1%)	0	1 (<1%)	0	0	0
APHTHOUS STOMATITIS	0	1 (<1%)	1 (<1%)	0	0	0
CONSTIPATION	2 (<1%)	0	2 (<1%)	0	0	0
DIARRHOEA	5 (<1%)	2 (1%)	7 (<1%)	0	0	3 (1%)
GASTROOESOPHAGEAL REFLUX DISEASE	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0
IRRITABLE BOWEL SYNDROME	1 (<1%)	0	1 (<1%)	0	0	0
NAUSEA	1 (<1%)	0	1 (<1%)	0	0	2 (1%)
ORAL DISORDER	0	0	0	1 (<1%)	0	0
STOMATITIS	1 (<1%)	0	1 (<1%)	0	0	0
TOOTHACHE	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
VOMITING	4 (<1%)	1 (<1%)	5 (<1%)	0	0	3 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	5 (<1%)	8 (2%)	13 (1%)	2 (<1%)	1 (<1%)	3 (1%)
CHEST PAIN	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
FATIGUE	0	0	0	1 (<1%)	0	0
GAIT DISTURBANCE	1 (<1%)	0	1 (<1%)	0	0	0
OEDEMA PERIPHERAL	1 (<1%)	0	1 (<1%)	0	0	0
PYREXIA	2 (<1%)	8 (2%)	10 (<1%)	0	1 (<1%)	3 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - AESUM_TRT_M26_11_18

Table 36.1

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	ACWYConVax (N=359)	Total ACWY (N=2498)	Menactra (N=539)	Menomune (N=209)	Tdap (N=353)
IMMUNE SYSTEM DISORDERS	4 (<1%)	0	4 (<1%)	0	2 (1%)	0
ALLERGIC OEDEMA	1 (<1%)	0	1 (<1%)	0	0	0
HYPERSENSITIVITY	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
SEASONAL ALLERGY	2 (<1%)	0	2 (<1%)	0	0	0
SELECTIVE IGM IMMUNODEFICIENCY	0	0	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	64 (3%)	30 (8%)	94 (4%)	5 (1%)	8 (4%)	22 (6%)
ABSCESS LIMB	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
APPENDICITIS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
BRONCHITIS	3 (<1%)	3 (1%)	6 (<1%)	0	0	0
BRONCHOPNEUMONIA	0	1 (<1%)	1 (<1%)	0	0	0
CANDIDIASIS	1 (<1%)	0	1 (<1%)	0	0	0
CELLULITIS	3 (<1%)	0	3 (<1%)	1 (<1%)	0	0
EAR INFECTION	2 (<1%)	1 (<1%)	3 (<1%)	0	0	2 (1%)
ERYTHEMA INFECTIOSUM	2 (<1%)	0	2 (<1%)	0	0	0
EXTERNAL EAR CELLULITIS	1 (<1%)	0	1 (<1%)	0	0	0
FOLLICULITIS	0	0	0	1 (<1%)	0	0
GASTROENTERITIS	2 (<1%)	3 (1%)	5 (<1%)	0	1 (<1%)	1 (<1%)
HERPES ZOSTER	2 (<1%)	0	2 (<1%)	0	0	0
IMPETIGO	0	1 (<1%)	1 (<1%)	0	0	0
INFECTIOUS MONONUCLEOSIS	2 (<1%)	0	2 (<1%)	0	0	0
INFLUENZA	9 (<1%)	8 (2%)	17 (1%)	0	1 (<1%)	7 (2%)
LARYNGITIS	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.1

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
...Continued from previous page						
INFECTIONS & INFESTATIONS						
LOCALISED INFECTION	0	0	0	2 (<1%)	0	0
LYMPH GLAND INFECTION	0	0	0	0	1 (<1%)	0
MYCOPLASMA INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
NAIL BED INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
NASOPHARYNGITIS	2 (<1%)	5 (1%)	7 (<1%)	0	0	2 (1%)
ORAL HERPES	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
OTITIS MEDIA	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
PARONYCHIA	2 (<1%)	0	2 (<1%)	0	0	0
PERITONSILLAR ABSCESS	2 (<1%)	0	2 (<1%)	0	0	0
PHARYNGITIS	9 (<1%)	9 (3%)	18 (1%)	0	1 (<1%)	10 (3%)
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	1 (<1%)	0	0	0
PNEUMONIA	3 (<1%)	0	3 (<1%)	0	0	0
PNEUMONIA PRIMARY ATYPICAL	0	0	0	0	1 (<1%)	0
RHINITIS	0	0	0	0	0	1 (<1%)
SIALOADENITIS	1 (<1%)	0	1 (<1%)	0	0	0
SINUSITIS	3 (<1%)	1 (<1%)	4 (<1%)	0	1 (<1%)	0
STAPHYLOCOCCAL INFECTION	3 (<1%)	0	3 (<1%)	1 (<1%)	0	0
TINEA VERSICOLOUR	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
TONSILLITIS	4 (<1%)	2 (1%)	6 (<1%)	0	0	3 (1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0

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Subjects ages 11-18 (Study V59P18 excluded)

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...Continued from previous page						
INFECTIONS & INFESTATIONS						
VARICELLA	3 (<1%)	0	3 (<1%)	0	0	0
VIRAL INFECTION	2 (<1%)	0	2 (<1%)	0	0	0
VIRAL PHARYNGITIS	0	0	0	1 (<1%)	0	0
VIRAL RASH	1 (<1%)	0	1 (<1%)	0	0	0
WOUND INFECTION	0	0	0	0	1 (<1%)	0
INJURY & POISONING	61 (3%)	2 (1%)	63 (3%)	16 (3%)	10 (5%)	2 (1%)
ACCIDENTAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
ARTHROPOD STING	0	0	0	1 (<1%)	0	0
BACK INJURY	1 (<1%)	0	1 (<1%)	0	0	0
CHEST INJURY	1 (<1%)	0	1 (<1%)	0	0	0
CLAVICLE FRACTURE	3 (<1%)	0	3 (<1%)	0	0	0
CONCUSSION	4 (<1%)	0	4 (<1%)	0	1 (<1%)	0
CONTUSION	8 (<1%)	0	8 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
DISLOCATION OF STERNUM	0	0	0	1 (<1%)	0	0
EPICONDYLITIS	1 (<1%)	0	1 (<1%)	0	0	0
FACIAL BONES FRACTURE	0	0	0	1 (<1%)	0	0
FEMUR FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
FOOT FRACTURE	6 (<1%)	0	6 (<1%)	1 (<1%)	0	0
FRACTURED COCCYX	0	0	0	0	0	1 (<1%)

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Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
...Continued from previous page						
INJURY & POISONING						
HAND FRACTURE	5 (<1%)	0	5 (<1%)	1 (<1%)	1 (<1%)	0
HEAD INJURY	2 (<1%)	0	2 (<1%)	0	0	0
HEAT STROKE	0	1 (<1%)	1 (<1%)	0	0	0
INJURY	2 (<1%)	0	2 (<1%)	0	0	0
INTENTIONAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
JAW FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
JOINT DISLOCATION	3 (<1%)	0	3 (<1%)	0	0	0
JOINT INJURY	3 (<1%)	0	3 (<1%)	1 (<1%)	0	0
JOINT SPRAIN	5 (<1%)	0	5 (<1%)	1 (<1%)	2 (1%)	0
LACERATION	1 (<1%)	0	1 (<1%)	0	0	0
LIGAMENT RUPTURE	2 (<1%)	0	2 (<1%)	0	0	0
LIMB INJURY	6 (<1%)	0	6 (<1%)	1 (<1%)	0	0
MENISCUS LESION	0	0	0	1 (<1%)	0	0
MUSCLE STRAIN	2 (<1%)	0	2 (<1%)	0	0	0
NECK INJURY	0	0	0	0	2 (1%)	0
OPEN WOUND	0	0	0	0	1 (<1%)	0
PELVIC FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
PROCEDURAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
RADIUS FRACTURE	0	1 (<1%)	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	0	2 (<1%)	0	0	0

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...Continued from previous page						
INJURY & POISONING						
SKIN LACERATION	2 (<1%)	0	2 (<1%)	3 (1%)	0	0
SPINAL COMPRESSION FRACTURE	0	0	0	1 (<1%)	0	0
STRESS FRACTURE	0	0	0	0	1 (<1%)	0
THERAPEUTIC AGENT TOXICITY	0	0	0	1 (<1%)	0	0
TRAUMATIC BRAIN INJURY	1 (<1%)	0	1 (<1%)	0	0	0
UPPER LIMB FRACTURE	0	0	0	0	1 (<1%)	0
WOUND	1 (<1%)	0	1 (<1%)	0	0	0
WRIST FRACTURE	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (1%)	0
INVESTIGATIONS	2 (<1%)	0	2 (<1%)	2 (<1%)	0	0
BLOOD CHOLESTEROL INCREASED	0	0	0	1 (<1%)	0	0
CARDIAC MURMUR	0	0	0	1 (<1%)	0	0
HEART RATE INCREASED	1 (<1%)	0	1 (<1%)	0	0	0
WEIGHT INCREASED	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
METABOLISM & NUTRITION DISORDERS	4 (<1%)	0	4 (<1%)	1 (<1%)	0	0
DEHYDRATION	2 (<1%)	0	2 (<1%)	0	0	0
HYPERINSULINISM	1 (<1%)	0	1 (<1%)	0	0	0
HYPERLIPIDAEMIA	1 (<1%)	0	1 (<1%)	0	0	0
HYPOKALAEMIA	0	0	0	1 (<1%)	0	0
METABOLIC SYNDROME	1 (<1%)	0	1 (<1%)	0	0	0

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Subjects ages 11-18 (Study V59P18 excluded)

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MUSCULO., CONNECT. TIS. & BONE DIS.	22 (1%)	2 (1%)	24 (1%)	9 (2%)	0	4 (1%)
ARTHRALGIA	8 (<1%)	0	8 (<1%)	4 (1%)	0	1 (<1%)
ARTHRITIS	1 (<1%)	0	1 (<1%)	0	0	0
BACK PAIN	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
BURSITIS	0	0	0	0	0	1 (<1%)
ENTHESOPATHY	1 (<1%)	0	1 (<1%)	0	0	0
EPIPHYSIOLYSIS	1 (<1%)	0	1 (<1%)	0	0	0
JOINT SWELLING	0	0	0	1 (<1%)	0	0
LUMBAR SPINE FLATTENING	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULOSKELETAL CHEST PAIN	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULOSKELETAL DISORDER	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULOSKELETAL PAIN	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
MYALGIA	0	1 (<1%)	1 (<1%)	0	0	2 (1%)
NECK PAIN	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
OSTEOCHONDROSIS	2 (<1%)	0	2 (<1%)	0	0	0
PAIN IN EXTREMITY	4 (<1%)	0	4 (<1%)	0	0	0
ROTATOR CUFF SYNDROME	2 (<1%)	0	2 (<1%)	0	0	0
TENDONITIS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	1 (<1%)	1 (<1%)	0	0	0
MELANOCYTIC NAEVUS	0	1 (<1%)	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	22 (1%)	6 (2%)	28 (1%)	4 (1%)	4 (2%)	2 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.1

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
...Continued from previous page						
NERVOUS SYSTEM DISORDERS						
ARACHNOID CYST	0	0	0	0	1 (<1%)	0
CARPAL TUNNEL SYNDROME	1 (<1%)	0	1 (<1%)	0	0	0
CONVULSION	1 (<1%)	0	1 (<1%)	0	0	0
DIZZINESS	4 (<1%)	0	4 (<1%)	0	0	0
HEADACHE	6 (<1%)	6 (2%)	12 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
HYPOAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0
MIGRAINE	2 (<1%)	0	2 (<1%)	2 (<1%)	1 (<1%)	0
MYASTHENIA GRAVIS	1 (<1%)	0	1 (<1%)	0	0	0
MYOCLONIC EPILEPSY	1 (<1%)	0	1 (<1%)	0	0	0
SYNCOPE	4 (<1%)	0	4 (<1%)	0	0	0
SYNCOPE VASOVAGAL	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0
TENSION HEADACHE	1 (<1%)	0	1 (<1%)	0	0	0
TREMOR	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	16 (1%)	0	16 (1%)	6 (1%)	5 (2%)	0
ALCOHOL ABUSE	1 (<1%)	0	1 (<1%)	0	0	0
ANXIETY	4 (<1%)	0	4 (<1%)	1 (<1%)	0	0
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	4 (<1%)	0	4 (<1%)	1 (<1%)	1 (<1%)	0
DEPRESSION	6 (<1%)	0	6 (<1%)	2 (<1%)	3 (1%)	0
HALLUCINATION, AUDITORY	0	0	0	0	1 (<1%)	0

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...Continued from previous page						
PSYCHIATRIC DISORDERS						
INSOMNIA	0	0	0	0	1 (<1%)	0
MAJOR DEPRESSION	0	0	0	1 (<1%)	0	0
SUICIDAL IDEATION	0	0	0	1 (<1%)	0	0
SUICIDE ATTEMPT	1 (<1%)	0	1 (<1%)	0	0	0
TIC	0	0	0	1 (<1%)	0	0
RENAL & URINARY DISORDERS	0	0	0	0	0	1 (<1%)
NEPHROLITHIASIS	0	0	0	0	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	5 (<1%)	0	5 (<1%)	2 (<1%)	1 (<1%)	0
DYSMENORRHOEA	3 (<1%)	0	3 (<1%)	1 (<1%)	0	0
FIBROCYSTIC BREAST DISEASE	1 (<1%)	0	1 (<1%)	0	0	0
MENORRHAGIA	0	0	0	1 (<1%)	0	0
OLIGOMENORRHOEA	0	0	0	0	1 (<1%)	0
TESTICULAR TORSION	1 (<1%)	0	1 (<1%)	0	0	0
RESP., THORACIC & MEDIASTINAL DIS.	20 (1%)	2 (1%)	22 (1%)	4 (1%)	3 (1%)	3 (1%)
ASTHMA	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
ASTHMA EXERCISE INDUCED	2 (<1%)	0	2 (<1%)	0	0	0
BRONCHIAL HYPERREACTIVITY	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0

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...Continued from previous page						
RESP., THORACIC & MEDIASTINAL DIS.						
BRONCHOSPASM	2 (<1%)	0	2 (<1%)	0	0	0
COUGH	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0
DYSPNOEA	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
EPISTAXIS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
HYPERVENTILATION	1 (<1%)	0	1 (<1%)	0	0	0
PARANASAL SINUS HYPERSECRETION	0	0	0	1 (<1%)	0	0
PHARYNGOLARYNGEAL PAIN	1 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)
RHINITIS ALLERGIC	7 (<1%)	0	7 (<1%)	1 (<1%)	0	0
RHINITIS SEASONAL	1 (<1%)	0	1 (<1%)	0	0	0
SNORING	1 (<1%)	0	1 (<1%)	0	0	0
WHEEZING	1 (<1%)	0	1 (<1%)	0	0	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	10 (<1%)	0	10 (<1%)	4 (1%)	1 (<1%)	2 (1%)
ACNE	0	0	0	1 (<1%)	0	1 (<1%)
DERMATITIS ATOPIC	1 (<1%)	0	1 (<1%)	0	0	0
DERMATITIS CONTACT	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
ERYTHEMA	0	0	0	0	1 (<1%)	0
HYPERHIDROSIS	2 (<1%)	0	2 (<1%)	0	0	0
INGROWING NAIL	1 (<1%)	0	1 (<1%)	0	0	0
PANNICULITIS	0	0	0	1 (<1%)	0	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.1

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Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
...Continued from previous page						
SKIN & SUBCUTANEOUS TIS. DISORDERS						
RASH	0	0	0	1 (<1%)	0	0
SKIN NODULE	1 (<1%)	0	1 (<1%)	0	0	0
URTICARIA	4 (<1%)	0	4 (<1%)	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	3 (<1%)	0	3 (<1%)	0	0	0
CYST REMOVAL	1 (<1%)	0	1 (<1%)	0	0	0
PERIODONTAL OPERATION	1 (<1%)	0	1 (<1%)	0	0	0
WISDOM TEETH REMOVAL	1 (<1%)	0	1 (<1%)	0	0	0
VASCULAR DISORDERS	0	0	0	1 (<1%)	0	0
PHLEBITIS	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	76 (7%)	40 (7%)
CARDIAC DISORDERS	0	2 (<1%)
PALPITATIONS	0	1 (<1%)
TACHYCARDIA	0	1 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0
VERTIGO	1 (<1%)	0
ENDOCRINE DISORDERS	1 (<1%)	0
HYPOTHYROIDISM	1 (<1%)	0
GASTROINTESTINAL DISORDERS	15 (1%)	4 (1%)
ABDOMINAL HERNIA	1 (<1%)	0
ABDOMINAL PAIN	2 (<1%)	4 (1%)
DIARRHOEA	1 (<1%)	0
GASTRITIS	5 (<1%)	0
GASTROOESOPHAGEAL REFLUX DISEASE	2 (<1%)	0
IRRITABLE BOWEL SYNDROME	3 (<1%)	0
MALLORY-WEISS SYNDROME	1 (<1%)	0
NAUSEA	1 (<1%)	0
TOOTHACHE	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
GEN. DISORDERS & ADMIN. SITE COND.	2 (<1%)	2 (<1%)
CHEST PAIN	0	1 (<1%)
GENERALISED OEDEMA	0	1 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0
MALAISE	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	2 (<1%)	1 (<1%)
DRUG HYPERSENSITIVITY	1 (<1%)	1 (<1%)
HYPERSENSITIVITY	1 (<1%)	0
INFECTIONS & INFESTATIONS	22 (2%)	9 (2%)
APPENDICITIS	1 (<1%)	0
BRONCHITIS	5 (<1%)	1 (<1%)
CELLULITIS	2 (<1%)	2 (<1%)
FUNGAL INFECTION	1 (<1%)	0
GENITAL HERPES	0	1 (<1%)
HELICOBACTER GASTRITIS	2 (<1%)	0
HERPES ZOSTER	0	1 (<1%)
PARASITIC GASTROENTERITIS	1 (<1%)	0
PHARYNGITIS	1 (<1%)	0
PILONIDAL CYST	0	1 (<1%)
PNEUMONIA	4 (<1%)	0
RHINITIS	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
INFECTIONS & INFESTATIONS		
SUBCUTANEOUS ABSCESS	2 (<1%)	0
TONSILLITIS	0	1 (<1%)
URINARY TRACT INFECTION	1 (<1%)	0
VAGINAL INFECTION	0	1 (<1%)
VAGINITIS BACTERIAL	1 (<1%)	0
VARICELLA	1 (<1%)	1 (<1%)
INJURY & POISONING	13 (1%)	8 (1%)
ARTHROPOD STING	1 (<1%)	0
BURNS SECOND DEGREE	0	1 (<1%)
CONTUSION	1 (<1%)	0
EXCORIATION	0	1 (<1%)
FOOT FRACTURE	1 (<1%)	0
FRACTURED COCCYX	1 (<1%)	0
GUN SHOT WOUND	0	1 (<1%)
HEAD INJURY	0	1 (<1%)
INJURY	1 (<1%)	1 (<1%)
JOINT DISLOCATION	1 (<1%)	1 (<1%)
JOINT SPRAIN	3 (<1%)	1 (<1%)
LACERATION	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
INJURY & POISONING		
MENISCUS LESION	0	1 (<1%)
OVERDOSE	1 (<1%)	0
PROCEDURAL PAIN	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
SOFT TISSUE INJURY	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	4 (<1%)	3 (1%)
BACK PAIN	2 (<1%)	2 (<1%)
MUSCLE SPASMS	2 (<1%)	0
PAIN IN EXTREMITY	0	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0
UTERINE LEIOMYOMA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	8 (1%)	6 (1%)
DIZZINESS	1 (<1%)	1 (<1%)
DYSTONIA	1 (<1%)	0
FACIAL PALSY	0	1 (<1%)
GRAND MAL CONVULSION	1 (<1%)	0
HEADACHE	2 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
MIGRAINE	2 (<1%)	1 (<1%)
PARAESTHESIA	1 (<1%)	0
PETIT MAL EPILEPSY	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)
TREMOR	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	4 (<1%)	0
ABORTION SPONTANEOUS	3 (<1%)	0
ABORTION THREATENED	1 (<1%)	0
PSYCHIATRIC DISORDERS	4 (<1%)	1 (<1%)
ANXIETY	3 (<1%)	0
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	0	1 (<1%)
CONVERSION DISORDER	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	0
RENAL & URINARY DISORDERS	0	1 (<1%)
NEPHROLITHIASIS	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	3 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
REPRODUCT. SYS. & BREAST DISORDERS		
OVARIAN CYST	1 (<1%)	0
VAGINAL DISCHARGE	1 (<1%)	0
VAGINAL HAEMORRHAGE	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	8 (1%)	3 (1%)
ASTHMA	3 (<1%)	0
ASTHMATIC CRISIS	1 (<1%)	0
BRONCHIAL HYPERREACTIVITY	1 (<1%)	0
BRONCHOSPASM	1 (<1%)	0
DYSPNOEA	1 (<1%)	0
PULMONARY EMBOLISM	1 (<1%)	0
RESPIRATORY FAILURE	1 (<1%)	0
RHINITIS ALLERGIC	0	3 (1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	3 (<1%)	2 (<1%)
ACNE	1 (<1%)	0
ANGIOEDEMA	0	1 (<1%)
DERMATITIS ALLERGIC	1 (<1%)	1 (<1%)
DERMATITIS CONTACT	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.2

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
SURGICAL & MEDICAL PROCEDURES	2 (<1%)	3 (1%)
HYSTERECTOMY	1 (<1%)	0
LIPOSUCTION	0	1 (<1%)
NEPHRECTOMY	1 (<1%)	0
SEPTOPLASTY	0	1 (<1%)
UMBILICAL HERNIA REPAIR	0	1 (<1%)
VASCULAR DISORDERS	0	1 (<1%)
CIRCULATORY COLLAPSE	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	115 (8%)	47 (7%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	2 (<1%)	2 (<1%)
ANAEMIA	2 (<1%)	1 (<1%)
DEFICIENCY ANAEMIA	0	1 (<1%)
CARDIAC DISORDERS	1 (<1%)	2 (<1%)
EXTRASYSTOLES	0	1 (<1%)
PALPITATIONS	1 (<1%)	0
TACHYCARDIA	0	2 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0
HYPOACUSIS	1 (<1%)	0
ENDOCRINE DISORDERS	1 (<1%)	3 (<1%)
HYPOTHYROIDISM	1 (<1%)	3 (<1%)
EYE DISORDERS	2 (<1%)	1 (<1%)
BLEPHARITIS	1 (<1%)	0
PTERYGIUM	0	1 (<1%)
RETINAL DETACHMENT	1 (<1%)	0
GASTROINTESTINAL DISORDERS	11 (1%)	5 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GASTROINTESTINAL DISORDERS		
ABDOMINAL DISCOMFORT	1 (<1%)	0
ABDOMINAL DISTENSION	1 (<1%)	0
DIVERTICULUM INTESTINAL	1 (<1%)	0
GASTRIC ULCER	1 (<1%)	0
GASTRITIS	5 (<1%)	3 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (<1%)	0
IRRITABLE BOWEL SYNDROME	1 (<1%)	1 (<1%)
TOOTHACHE	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	6 (<1%)	1 (<1%)
CHEST PAIN	2 (<1%)	0
FATIGUE	2 (<1%)	0
HERNIA	1 (<1%)	0
MALAISE	1 (<1%)	0
PYREXIA	0	1 (<1%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0
GALLBLADDER POLYP	1 (<1%)	0
HEPATOMEGALY	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
INFECTIONS & INFESTATIONS	24 (2%)	6 (1%)
ABSCESS LIMB	1 (<1%)	0
BRONCHITIS	4 (<1%)	0
CELLULITIS	3 (<1%)	0
CONJUNCTIVITIS BACTERIAL	1 (<1%)	0
CYSTITIS	1 (<1%)	0
EYE INFECTION TOXOPLASMAL	0	1 (<1%)
GASTROENTERITIS VIRAL	1 (<1%)	0
HERPES ZOSTER	2 (<1%)	0
HIV INFECTION	0	1 (<1%)
KIDNEY INFECTION	1 (<1%)	0
MENINGITIS VIRAL	1 (<1%)	0
PERIORBITAL CELLULITIS	1 (<1%)	0
PHARYNGITIS	1 (<1%)	0
PNEUMONIA	5 (<1%)	0
SINUSITIS	1 (<1%)	0
SUBCUTANEOUS ABSCESS	1 (<1%)	2 (<1%)
TOOTH ABSCESS	1 (<1%)	0
URINARY TRACT INFECTION	1 (<1%)	1 (<1%)
VULVOVAGINITIS TRICHOMONAL	1 (<1%)	1 (<1%)
INJURY & POISONING	14 (1%)	7 (1%)
ANIMAL BITE	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
INJURY & POISONING		
ANKLE FRACTURE	0	1 (<1%)
BACK INJURY	0	1 (<1%)
CLAVICLE FRACTURE	1 (<1%)	0
FALL	1 (<1%)	1 (<1%)
HEAD INJURY	1 (<1%)	0
INJURY	7 (<1%)	1 (<1%)
JOINT INJURY	1 (<1%)	0
JOINT SPRAIN	0	1 (<1%)
RADIUS FRACTURE	1 (<1%)	0
SKIN LACERATION	1 (<1%)	0
UPPER LIMB FRACTURE	1 (<1%)	1 (<1%)
WOUND	0	1 (<1%)
INVESTIGATIONS	4 (<1%)	0
ENDOSCOPY	1 (<1%)	0
LIVER FUNCTION TEST ABNORMAL	1 (<1%)	0
TRANSAMINASES INCREASED	1 (<1%)	0
WEIGHT DECREASED	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	8 (1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
METABOLISM & NUTRITION DISORDERS		
DYSLIPIDAEMIA	4 (<1%)	0
HYPERCHOLESTEROLAEMIA	2 (<1%)	1 (<1%)
HYPERLIPIDAEMIA	2 (<1%)	0
TYPE 2 DIABETES MELLITUS	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	18 (1%)	8 (1%)
ARTHRALGIA	1 (<1%)	0
BACK PAIN	2 (<1%)	3 (<1%)
COSTOCHONDRITIS	1 (<1%)	0
EXOSTOSIS	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	2 (<1%)	2 (<1%)
JOINT SWELLING	1 (<1%)	0
MUSCLE SPASMS	0	1 (<1%)
MUSCULOSKELETAL PAIN	3 (<1%)	0
MYALGIA	1 (<1%)	0
OSTEOARTHRITIS	1 (<1%)	2 (<1%)
PAIN IN EXTREMITY	1 (<1%)	0
PLANTAR FASCIITIS	1 (<1%)	0
SYNOVIAL CYST	1 (<1%)	0
TEMPOROMANDIBULAR JOINT SYNDROME	1 (<1%)	0
TENDONITIS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	4 (<1%)	2 (<1%)
ACROCHORDON	1 (<1%)	0
BREAST NEOPLASM	0	1 (<1%)
MELANOCYTIC NAEVUS	1 (<1%)	0
MORTON'S NEUROMA	1 (<1%)	0
PAPILLOMA	1 (<1%)	0
UTERINE LEIOMYOMA	1 (<1%)	1 (<1%)
NERVOUS SYSTEM DISORDERS	7 (<1%)	6 (1%)
CARPAL TUNNEL SYNDROME	1 (<1%)	0
DIZZINESS	0	1 (<1%)
EPILEPSY	1 (<1%)	0
HEADACHE	0	3 (<1%)
MIGRAINE	1 (<1%)	2 (<1%)
POST HERPETIC NEURALGIA	0	1 (<1%)
SOMNOLENCE	0	1 (<1%)
SYNCOPE	2 (<1%)	0
TENSION HEADACHE	2 (<1%)	0
TREMOR	0	1 (<1%)
PSYCHIATRIC DISORDERS	5 (<1%)	1 (<1%)
ANXIETY	2 (<1%)	0
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
PSYCHIATRIC DISORDERS		
DEPRESSION	2 (<1%)	0
MENOPAUSAL DEPRESSION	1 (<1%)	0
RENAL & URINARY DISORDERS	2 (<1%)	2 (<1%)
HAEMATURIA	1 (<1%)	0
NEPHROLITHIASIS	1 (<1%)	1 (<1%)
RENAL COLIC	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	5 (<1%)	3 (<1%)
BREAST MASS	1 (<1%)	0
BREAST PAIN	1 (<1%)	1 (<1%)
ERECTILE DYSFUNCTION	0	1 (<1%)
MENOPAUSAL SYMPTOMS	1 (<1%)	0
OVARIAN CYST	2 (<1%)	0
VAGINAL DISCHARGE	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	6 (<1%)	1 (<1%)
ASTHMA	1 (<1%)	0
ASTHMATIC CRISIS	1 (<1%)	0
BRONCHOSPASM	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 36.3

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
RESP., THORACIC & MEDIASTINAL DIS.		
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (<1%)
DYSPNOEA	1 (<1%)	0
LARYNGITIS ALLERGIC	1 (<1%)	0
RHINITIS ALLERGIC	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	2 (<1%)	2 (<1%)
ALOPECIA	0	1 (<1%)
DERMATITIS	1 (<1%)	0
PSORIASIS	1 (<1%)	0
URTICARIA	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	2 (<1%)	0
HYSTERECTOMY	1 (<1%)	0
ROTATOR CUFF REPAIR	1 (<1%)	0
VASCULAR DISORDERS	7 (<1%)	3 (<1%)
DEEP VEIN THROMBOSIS	1 (<1%)	0
HOT FLUSH	1 (<1%)	0
HYPERTENSION	4 (<1%)	2 (<1%)
HYPERTENSIVE CRISIS	1 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 37

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	29 (1%)	12 (1%)	18 (1%)	59 (1%)	16 (1%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	0	1 (<1%)	0	1 (<1%)	0
LYMPH NODE PAIN	0	1 (<1%)	0	1 (<1%)	0
EAR & LABYRINTH DISORDERS	1 (<1%)	0	0	1 (<1%)	0
VERTIGO	1 (<1%)	0	0	1 (<1%)	0
GASTROINTESTINAL DISORDERS	5 (<1%)	2 (<1%)	1 (<1%)	8 (<1%)	1 (<1%)
DIARRHOEA	1 (<1%)	0	0	1 (<1%)	0
GASTRITIS	1 (<1%)	0	0	1 (<1%)	0
NAUSEA	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
VOMITING	1 (<1%)	0	0	1 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	3 (<1%)	5 (<1%)	11 (<1%)	1 (<1%)
AXILLARY PAIN	0	0	1 (<1%)	1 (<1%)	0
CHILLS	1 (<1%)	0	0	1 (<1%)	0
INDURATION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
MALAISE	1 (<1%)	2 (<1%)	3 (<1%)	6 (<1%)	1 (<1%)
OEDEMA PERIPHERAL	0	0	1 (<1%)	1 (<1%)	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0	0	1 (<1%)	0
HEPATITIS	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESUM_SEV_ACWY_M1

Table 37

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
INFECTIONS & INFESTATIONS	5 (<1%)	1 (<1%)	4 (<1%)	10 (<1%)	5 (<1%)
CELLULITIS	1 (<1%)	0	0	1 (<1%)	0
GASTROENTERITIS	0	0	1 (<1%)	1 (<1%)	1 (<1%)
GASTROENTERITIS VIRAL	1 (<1%)	0	0	1 (<1%)	0
HERPES ZOSTER	0	0	0	0	1 (<1%)
INFLUENZA	1 (<1%)	0	0	1 (<1%)	0
NASOPHARYNGITIS	0	0	1 (<1%)	1 (<1%)	0
OTITIS MEDIA	0	1 (<1%)	0	1 (<1%)	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	1 (<1%)	2 (<1%)	0
SINUSITIS	0	0	1 (<1%)	1 (<1%)	0
TOOTH INFECTION	0	0	0	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	0	1 (<1%)	1 (<1%)
URINARY TRACT INFECTION	0	0	0	0	1 (<1%)
INJURY & POISONING	5 (<1%)	0	1 (<1%)	6 (<1%)	2 (<1%)
ALCOHOL POISONING	1 (<1%)	0	0	1 (<1%)	0
ANKLE FRACTURE	0	0	0	0	1 (<1%)
ARTHROPOD BITE	1 (<1%)	0	0	1 (<1%)	0
CONTUSION	0	0	1 (<1%)	1 (<1%)	0
FALL	0	0	0	0	1 (<1%)
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	0	1 (<1%)	0
RADIUS FRACTURE	1 (<1%)	0	0	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	0	0	1 (<1%)	1 (<1%)	0
TIBIA FRACTURE	1 (<1%)	0	0	1 (<1%)	0
WOUND	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESUM_SEV_ACWY_M1

Table 37

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
MUSCULO., CONNECT. TIS. & BONE DIS.	3 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	3 (<1%)
ARTHRALGIA	0	0	3 (<1%)	3 (<1%)	2 (<1%)
BACK PAIN	0	0	1 (<1%)	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (<1%)
MUSCLE SPASMS	0	1 (<1%)	0	1 (<1%)	0
MYALGIA	2 (<1%)	0	1 (<1%)	3 (<1%)	1 (<1%)
PAIN IN EXTREMITY	1 (<1%)	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	6 (<1%)	8 (1%)	6 (<1%)	20 (<1%)	6 (<1%)
HEADACHE	5 (<1%)	5 (<1%)	4 (<1%)	14 (<1%)	4 (<1%)
MIGRAINE	0	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
SCIATICA	0	0	0	0	1 (<1%)
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	0	1 (<1%)	0
SINUS HEADACHE	0	0	1 (<1%)	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	3 (<1%)	0	1 (<1%)	4 (<1%)	0
DEPRESSION	2 (<1%)	0	1 (<1%)	3 (<1%)	0
DEPRESSION SUICIDAL	1 (<1%)	0	0	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	0	0	1 (<1%)	0
DYSMENORRHOEA	1 (<1%)	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESUM_SEV_ACWY_M1

Table 37

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
SKIN & SUBCUTANEOUS TIS. DISORDERS					
ANGIOEDEMA	0	0	0	0	1 (<1%)
DERMATITIS CONTACT	1 (<1%)	0	0	1 (<1%)	0
ERYTHEMA	0	0	1 (<1%)	1 (<1%)	0
RASH	0	0	1 (<1%)	1 (<1%)	0
URTICARIA	0	0	1 (<1%)	1 (<1%)	0
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	0	1 (<1%)	0
ENDODONTIC PROCEDURE	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESUM_SEV_ACWY_M1

Table 38.1

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	24 (1%)	5 (1%)	29 (1%)	5 (1%)	4 (2%)	6 (1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
VERTIGO	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	4 (<1%)	1 (<1%)	5 (<1%)	0	0	1 (<1%)
DIARRHOEA	1 (<1%)	0	1 (<1%)	0	0	0
GASTRITIS	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
NAUSEA	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
VOMITING	1 (<1%)	0	1 (<1%)	0	0	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	0	3 (<1%)	0	0	0
CHILLS	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE PAIN	1 (<1%)	0	1 (<1%)	0	0	0
MALAISE	1 (<1%)	0	1 (<1%)	0	0	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
HEPATITIS	1 (<1%)	0	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	3 (<1%)	2 (<1%)	5 (<1%)	3 (1%)	2 (1%)	1 (<1%)
CELLULITIS	0	1 (<1%)	1 (<1%)	0	0	0
GASTROENTERITIS	0	0	0	1 (<1%)	0	0
GASTROENTERITIS VIRAL	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_11_18.SAS(WARTERO) 10JUL08, 08:17 SAS.9.1 - AESUM_SEV_TRT_M1_11_18

Table 38.1

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
INFECTIONS & INFESTATIONS						
INFLUENZA	0	1 (<1%)	1 (<1%)	0	0	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
SINUSITIS	0	0	0	0	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0
URINARY TRACT INFECTION	0	0	0	1 (<1%)	0	0
INJURY & POISONING	5 (<1%)	0	5 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
ALCOHOL POISONING	1 (<1%)	0	1 (<1%)	0	0	0
ANKLE FRACTURE	0	0	0	1 (<1%)	0	0
ARTHROPOD BITE	1 (<1%)	0	1 (<1%)	0	0	0
CONCUSSION	0	0	0	0	1 (<1%)	0
INJURY	0	0	0	0	0	1 (<1%)
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	1 (<1%)	0	0	0
RADIUS FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
TIBIA FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	3 (<1%)	0	3 (<1%)	0	0	1 (<1%)
MYALGIA	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)
PAIN IN EXTREMITY	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_11_18.SAS(WARTERO) 10JUL08, 08:17 SAS.9.1 - AESUM_SEV_TRT_M1_11_18

Table 38.1

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
NERVOUS SYSTEM DISORDERS	5 (<1%)	1 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
AMNESIA	0	0	0	0	0	1 (<1%)
DIZZINESS	0	0	0	0	0	1 (<1%)
HEADACHE	4 (<1%)	1 (<1%)	5 (<1%)	0	1 (<1%)	1 (<1%)
MIGRAINE	0	0	0	1 (<1%)	0	0
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
DEPRESSION	2 (<1%)	0	2 (<1%)	0	0	0
DEPRESSION SUICIDAL	1 (<1%)	0	1 (<1%)	0	0	0
REPRODUCT. SYS. & BREAST DISORDERS	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)
DYSMENORRHOEA	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	0	0	0	0	0	1 (<1%)
COUGH	0	0	0	0	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
DERMATITIS CONTACT	1 (<1%)	0	1 (<1%)	0	0	0
SURGICAL & MEDICAL PROCEDURES	0	1 (<1%)	1 (<1%)	0	0	0
ENDODONTIC PROCEDURE	0	1 (<1%)	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_11_18.SAS(WARTERO) 10JUL08, 08:17 SAS.9.1 - AESUM_SEV_TRT_M1_11_18

Table 38.2

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	12 (1%)	3 (1%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	1 (<1%)	0
LYMPH NODE PAIN	1 (<1%)	0
GASTROINTESTINAL DISORDERS	2 (<1%)	0
NAUSEA	2 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0
MALAISE	2 (<1%)	0
INFECTIONS & INFESTATIONS	1 (<1%)	0
OTITIS MEDIA	1 (<1%)	0
INJURY & POISONING	0	1 (<1%)
FALL	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0
MUSCLE SPASMS	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	8 (1%)	1 (<1%)
HEADACHE	5 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_19_34.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M1_19_34

Table 38.2

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
MIGRAINE	2 (<1%)	0
SYNCOPE VASOVAGAL	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)
ANGIOEDEMA	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_19_34.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M1_19_34

Table 38.3

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	18 (1%)	8 (1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	1 (<1%)
NAUSEA	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	5 (<1%)	1 (<1%)
AXILLARY PAIN	1 (<1%)	0
INDURATION	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0
MALAISE	3 (<1%)	1 (<1%)
OEDEMA PERIPHERAL	1 (<1%)	0
INFECTIONS & INFESTATIONS	4 (<1%)	2 (<1%)
GASTROENTERITIS	1 (<1%)	0
HERPES ZOSTER	0	1 (<1%)
NASOPHARYNGITIS	1 (<1%)	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0
SINUSITIS	1 (<1%)	0
TOOTH INFECTION	0	1 (<1%)
INJURY & POISONING	1 (<1%)	0
CONTUSION	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
WOUND	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_35_55.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M1_35_55

Table 38.3

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
MUSCULO., CONNECT. TIS. & BONE DIS.	4 (<1%)	3 (<1%)
ARTHRALGIA	3 (<1%)	2 (<1%)
BACK PAIN	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)
MYALGIA	1 (<1%)	1 (<1%)
NERVOUS SYSTEM DISORDERS	6 (<1%)	4 (1%)
HEADACHE	4 (<1%)	3 (<1%)
MIGRAINE	1 (<1%)	0
SCIATICA	0	1 (<1%)
SINUS HEADACHE	1 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	0
DEPRESSION	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	2 (<1%)	0
ERYTHEMA	1 (<1%)	0
RASH	1 (<1%)	0
URTICARIA	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_35_55.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M1_35_55

Table 39

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)
ANY ADVERSE EVENT	23 (1%)	9 (1%)	10 (1%)	42 (1%)	14 (1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
HYPOACUSIS	0	0	1 (<1%)	1 (<1%)	0
VERTIGO	1 (<1%)	0	0	1 (<1%)	0
EYE DISORDERS	0	0	1 (<1%)	1 (<1%)	0
RETINAL DETACHMENT	0	0	1 (<1%)	1 (<1%)	0
GASTROINTESTINAL DISORDERS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
ABDOMINAL PAIN	1 (<1%)	0	0	1 (<1%)	0
NAUSEA	0	1 (<1%)	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	5 (<1%)	3 (<1%)	4 (<1%)	12 (<1%)	1 (<1%)
APPENDICITIS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
BRONCHITIS	0	0	1 (<1%)	1 (<1%)	0
CELLULITIS	0	0	0	0	1 (<1%)
INFECTIOUS MONONUCLEOSIS	1 (<1%)	0	0	1 (<1%)	0
KIDNEY INFECTION	0	0	1 (<1%)	1 (<1%)	0
MENINGITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0
PNEUMONIA	0	2 (<1%)	2 (<1%)	4 (<1%)	0
TONSILLITIS	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M26.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_ACWY_M26

Table 39

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
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INFECTIONS & INFESTATIONS					
VARICELLA	1 (<1%)	0	0	1 (<1%)	0
VIRAL RASH	1 (<1%)	0	0	1 (<1%)	0
INJURY & POISONING	13 (1%)	2 (<1%)	1 (<1%)	16 (<1%)	7 (<1%)
ACCIDENTAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
ANKLE FRACTURE	0	0	0	0	1 (<1%)
BURNS SECOND DEGREE	0	0	0	0	1 (<1%)
CLAVICLE FRACTURE	2 (<1%)	0	0	2 (<1%)	0
DISLOCATION OF STERNUM	0	0	0	0	1 (<1%)
FACIAL BONES FRACTURE	0	0	0	0	1 (<1%)
FEMUR FRACTURE	1 (<1%)	0	0	1 (<1%)	0
FOOT FRACTURE	0	0	0	0	1 (<1%)
HEAD INJURY	1 (<1%)	0	0	1 (<1%)	0
HEAT STROKE	1 (<1%)	0	0	1 (<1%)	0
INTENTIONAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
JOINT DISLOCATION	1 (<1%)	0	0	1 (<1%)	0
LIGAMENT RUPTURE	2 (<1%)	0	0	2 (<1%)	0
MENISCUS LESION	0	0	0	0	1 (<1%)
OVERDOSE	0	1 (<1%)	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M26.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_ACWY_M26

Table 39

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INJURY & POISONING					
ROAD TRAFFIC ACCIDENT	1 (<1%)	1 (<1%)	0	2 (<1%)	0
SPINAL COMPRESSION FRACTURE	0	0	0	0	1 (<1%)
THERAPEUTIC AGENT TOXICITY	0	0	0	0	1 (<1%)
TRAUMATIC BRAIN INJURY	1 (<1%)	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	1 (<1%)	0
WRIST FRACTURE	1 (<1%)	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	0	1 (<1%)	1 (<1%)
EPIPHYSIOLYSIS	1 (<1%)	0	0	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	0	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
DYSTONIA	0	1 (<1%)	0	1 (<1%)	0
GRAND MAL CONVULSION	0	1 (<1%)	0	1 (<1%)	0
POST HERPETIC NEURALGIA	0	0	0	0	1 (<1%)
SYNCOPE	0	0	1 (<1%)	1 (<1%)	0
SYNCOPE VASOVAGAL	0	0	0	0	1 (<1%)
TREMOR	0	0	0	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	0	2 (<1%)	0	2 (<1%)	0
ABORTION SPONTANEOUS	0	2 (<1%)	0	2 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M26.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_ACWY_M26

Table 39

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
PSYCHIATRIC DISORDERS	2 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)
ALCOHOL ABUSE	1 (<1%)	0	0	1 (<1%)	0
DEPRESSION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
MAJOR DEPRESSION	0	0	0	0	1 (<1%)
SUICIDE ATTEMPT	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RENAL & URINARY DISORDERS	0	0	0	0	2 (<1%)
NEPHROLITHIASIS	0	0	0	0	1 (<1%)
RENAL COLIC	0	0	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	0	2 (<1%)	0	2 (<1%)	0
PULMONARY EMBOLISM	0	1 (<1%)	0	1 (<1%)	0
RESPIRATORY FAILURE	0	1 (<1%)	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	0	1 (<1%)
URTICARIA	0	0	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	1 (<1%)	2 (<1%)	0
PERIODONTAL OPERATION	1 (<1%)	0	0	1 (<1%)	0
ROTATOR CUFF REPAIR	0	0	1 (<1%)	1 (<1%)	0
VASCULAR DISORDERS	0	0	0	0	1 (<1%)
CIRCULATORY COLLAPSE	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M26.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_ACWY_M26

Table 40.1

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
ANY ADVERSE EVENT	22 (1%)	1 (<1%)	23 (1%)	5 (1%)	10 (5%)	1 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
VERTIGO	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
ABDOMINAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
ABDOMINAL PAIN LOWER	0	0	0	0	1 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	0	0	0	0	1 (<1%)	0
PYREXIA	0	0	0	0	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	0	0	0	0	1 (<1%)	0
HYPERSENSITIVITY	0	0	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	5 (<1%)	0	5 (<1%)	0	3 (1%)	0
APPENDICITIS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
INFECTIOUS MONONUCLEOSIS	1 (<1%)	0	1 (<1%)	0	0	0
PNEUMONIA PRIMARY ATYPICAL	0	0	0	0	1 (<1%)	0
TONSILLITIS	1 (<1%)	0	1 (<1%)	0	0	0
VARICELLA	1 (<1%)	0	1 (<1%)	0	0	0
VIRAL RASH	1 (<1%)	0	1 (<1%)	0	0	0
WOUND INFECTION	0	0	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M26_11_18

Table 40.1

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
INJURY & POISONING	12 (1%)	1 (<1%)	13 (1%)	4 (1%)	0	0
ACCIDENTAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
CLAVICLE FRACTURE	2 (<1%)	0	2 (<1%)	0	0	0
DISLOCATION OF STERNUM	0	0	0	1 (<1%)	0	0
FACIAL BONES FRACTURE	0	0	0	1 (<1%)	0	0
FEMUR FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
FOOT FRACTURE	0	0	0	1 (<1%)	0	0
HEAD INJURY	1 (<1%)	0	1 (<1%)	0	0	0
HEAT STROKE	0	1 (<1%)	1 (<1%)	0	0	0
INTENTIONAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
JOINT DISLOCATION	1 (<1%)	0	1 (<1%)	0	0	0
LIGAMENT RUPTURE	2 (<1%)	0	2 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	1 (<1%)	0	0	0
SPINAL COMPRESSION FRACTURE	0	0	0	1 (<1%)	0	0
THERAPEUTIC AGENT TOXICITY	0	0	0	1 (<1%)	0	0
TRAUMATIC BRAIN INJURY	1 (<1%)	0	1 (<1%)	0	0	0
WRIST FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	1 (<1%)	0	0	0
EPIPHYSIOLYSIS	1 (<1%)	0	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	0	2 (1%)	0
ARACHNOID CYST	0	0	0	0	1 (<1%)	0
SYNCOPE VASOVAGAL	0	0	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M26_11_18

Table 40.1

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
PSYCHIATRIC DISORDERS	2 (<1%)	0	2 (<1%)	2 (<1%)	1 (<1%)	0
ALCOHOL ABUSE	1 (<1%)	0	1 (<1%)	0	0	0
DEPRESSION	0	0	0	1 (<1%)	0	0
HALLUCINATION, AUDITORY	0	0	0	0	1 (<1%)	0
MAJOR DEPRESSION	0	0	0	1 (<1%)	0	0
SUICIDE ATTEMPT	1 (<1%)	0	1 (<1%)	0	0	0
RENAL & URINARY DISORDERS	0	0	0	0	0	1 (<1%)
NEPHROLITHIASIS	0	0	0	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	0	0	0	0	1 (<1%)	0
COUGH	0	0	0	0	1 (<1%)	0
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	1 (<1%)	0	0	0
PERIODONTAL OPERATION	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - AESUM_SEV_TRT_M26_11_18

Table 40.2

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	9 (1%)	3 (1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	0
NAUSEA	1 (<1%)	0
INFECTIONS & INFESTATIONS	3 (<1%)	1 (<1%)
APPENDICITIS	1 (<1%)	0
CELLULITIS	0	1 (<1%)
PNEUMONIA	2 (<1%)	0
INJURY & POISONING	2 (<1%)	2 (<1%)
BURNS SECOND DEGREE	0	1 (<1%)
MENISCUS LESION	0	1 (<1%)
OVERDOSE	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	2 (<1%)	1 (<1%)
DYSTONIA	1 (<1%)	0
GRAND MAL CONVULSION	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	2 (<1%)	0
ABORTION SPONTANEOUS	2 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - AESUM_SEV_TRT_M26_19_34

Table 40.2

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
PSYCHIATRIC DISORDERS		
SUICIDE ATTEMPT	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	2 (<1%)	0
PULMONARY EMBOLISM	1 (<1%)	0
RESPIRATORY FAILURE	1 (<1%)	0
VASCULAR DISORDERS	0	1 (<1%)
CIRCULATORY COLLAPSE	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - AESUM_SEV_TRT_M26_19_34

Table 40.3

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	10 (1%)	6 (1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0
HYPOACUSIS	1 (<1%)	0
EYE DISORDERS	1 (<1%)	0
RETINAL DETACHMENT	1 (<1%)	0
INFECTIONS & INFESTATIONS	4 (<1%)	0
BRONCHITIS	1 (<1%)	0
KIDNEY INFECTION	1 (<1%)	0
MENINGITIS VIRAL	1 (<1%)	0
PNEUMONIA	2 (<1%)	0
INJURY & POISONING	1 (<1%)	1 (<1%)
ANKLE FRACTURE	0	1 (<1%)
UPPER LIMB FRACTURE	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	1 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)
POST HERPETIC NEURALGIA	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - AESUM_SEV_TRT_M26_35_55

Table 40.3

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
SYNCOPE	1 (<1%)	0
TREMOR	0	1 (<1%)
PSYCHIATRIC DISORDERS	1 (<1%)	0
DEPRESSION	1 (<1%)	0
RENAL & URINARY DISORDERS	0	2 (<1%)
NEPHROLITHIASIS	0	1 (<1%)
RENAL COLIC	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)
URTICARIA	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0
ROTATOR CUFF REPAIR	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - AESUM_SEV_TRT_M26_35_55

Table 41

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups

MedDRA Preferred Term	Number (%) of Subjects[1]				
	Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
HEADACHE	24 (1%)	18 (2%)	20 (1%)	62 (1%)	20 (1%)
INJECTION SITE ERYTHEMA	11 (<1%)	12 (1%)	9 (1%)	32 (1%)	2 (<1%)
MALAISE	12 (<1%)	8 (1%)	14 (1%)	34 (1%)	5 (<1%)
INJECTION SITE PAIN	6 (<1%)	9 (1%)	13 (1%)	28 (<1%)	8 (<1%)
MYALGIA	7 (<1%)	3 (<1%)	13 (1%)	23 (<1%)	7 (<1%)
INJECTION SITE PRURITUS	10 (<1%)	3 (<1%)	12 (1%)	25 (<1%)	5 (<1%)
NAUSEA	12 (<1%)	8 (1%)	3 (<1%)	23 (<1%)	3 (<1%)
DIZZINESS	0	6 (1%)	4 (<1%)	10 (<1%)	12 (1%)
ARTHRALGIA	6 (<1%)	4 (<1%)	8 (1%)	18 (<1%)	11 (1%)
DIARRHOEA	4 (<1%)	7 (1%)	2 (<1%)	13 (<1%)	5 (<1%)
ERYTHEMA	5 (<1%)	1 (<1%)	8 (1%)	14 (<1%)	4 (<1%)
INJECTION SITE INDURATION	9 (<1%)	6 (1%)	6 (<1%)	21 (<1%)	1 (<1%)
LYMPHADENOPATHY	3 (<1%)	3 (<1%)	7 (<1%)	13 (<1%)	2 (<1%)
BACK PAIN	0	2 (<1%)	6 (<1%)	8 (<1%)	1 (<1%)
FATIGUE	1 (<1%)	2 (<1%)	6 (<1%)	9 (<1%)	2 (<1%)
NASOPHARYNGITIS	2 (<1%)	4 (<1%)	6 (<1%)	12 (<1%)	5 (<1%)
PHARYNGOLARYNGEAL PAIN	4 (<1%)	0	6 (<1%)	10 (<1%)	5 (<1%)
RASH	3 (<1%)	4 (<1%)	6 (<1%)	13 (<1%)	5 (<1%)
INDURATION	4 (<1%)	1 (<1%)	5 (<1%)	10 (<1%)	2 (<1%)
VOMITING	4 (<1%)	1 (<1%)	1 (<1%)	6 (<1%)	5 (<1%)
CHILLS	3 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	1 (<1%)
INJECTION SITE WARMTH	3 (<1%)	2 (<1%)	4 (<1%)	9 (<1%)	3 (<1%)
NECK PAIN	0	0	4 (<1%)	4 (<1%)	0
MIGRAINE	0	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)
VIRAL INFECTION	1 (<1%)	3 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
ABDOMINAL PAIN	3 (<1%)	1 (<1%)	1 (<1%)	5 (<1%)	4 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M1.SAS(WARTERO) 10JUL08, 08:55 SAS.9.1 - PRAESUMFRQ_ACWY_M1

Table 41

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups

MedDRA Preferred Term	Number (%) of Subjects[1]				
	Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
PARAESTHESIA	0	2 (<1%)	3 (<1%)	5 (<1%)	1 (<1%)
PAIN	7 (<1%)	0	2 (<1%)	9 (<1%)	0
SOMNOLENCE	1 (<1%)	2 (<1%)	2 (<1%)	5 (<1%)	2 (<1%)
SYNCOPE VASOVAGAL	0	2 (<1%)	0	2 (<1%)	1 (<1%)
VERTIGO	0	2 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
PAIN IN EXTREMITY	5 (<1%)	0	1 (<1%)	6 (<1%)	3 (<1%)
SYNCOPE	1 (<1%)	0	1 (<1%)	2 (<1%)	3 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
INJECTION SITE SWELLING	5 (<1%)	1 (<1%)	0	6 (<1%)	0
ABDOMINAL PAIN UPPER	2 (<1%)	1 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)
AXILLARY PAIN	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	0
FLUSHING	0	0	2 (<1%)	2 (<1%)	2 (<1%)
GASTROENTERITIS	0	1 (<1%)	2 (<1%)	3 (<1%)	0
HYPERHIDROSIS	0	0	2 (<1%)	2 (<1%)	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	2 (<1%)	3 (<1%)	0
INJECTION SITE HAEMORRHAGE	0	0	2 (<1%)	2 (<1%)	1 (<1%)
INSOMNIA	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)
PHARYNGITIS	4 (<1%)	0	2 (<1%)	6 (<1%)	0
PYREXIA	4 (<1%)	0	2 (<1%)	6 (<1%)	0
TINNITUS	0	0	2 (<1%)	2 (<1%)	0
URTICARIA	0	0	2 (<1%)	2 (<1%)	0
ASTHENIA	1 (<1%)	0	0	1 (<1%)	2 (<1%)
COUGH	2 (<1%)	0	0	2 (<1%)	2 (<1%)
INCREASED APPETITE	0	0	0	0	2 (<1%)
INJECTION SITE BRUISING	4 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
MUSCULOSKELETAL PAIN	0	0	1 (<1%)	1 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M1.SAS(WARTERO) 10JUL08, 08:55 SAS.9.1 - PRAESUMFRQ_ACWY_M1

Table 41

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
CELLULITIS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
CHEST PAIN	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
DYSMENORRHOEA	1 (<1%)	1 (<1%)	0	2 (<1%)	0
EAR PAIN	0	1 (<1%)	0	1 (<1%)	1 (<1%)
ECCHYMOSIS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
INJECTION SITE OEDEMA	0	1 (<1%)	1 (<1%)	2 (<1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	0	1 (<1%)	0	1 (<1%)	0
MUSCULAR WEAKNESS	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
ORAL HERPES	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
PRURITUS	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
SINUS HEADACHE	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
STOMACH DISCOMFORT	0	1 (<1%)	1 (<1%)	2 (<1%)	0
BURNING SENSATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
DEPRESSION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
DERMATITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)	0
DYSPEPSIA	0	0	1 (<1%)	1 (<1%)	0
EYE SWELLING	0	0	1 (<1%)	1 (<1%)	0
GASTROENTERITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0
HEAT EXHAUSTION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE INFECTION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE IRRITATION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE MASS	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE REACTION	0	0	1 (<1%)	1 (<1%)	0
MUSCULOSKELETAL STIFFNESS	0	0	1 (<1%)	1 (<1%)	0
OEDEMA PERIPHERAL	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M1.SAS(WARTERO) 10JUL08, 08:55 SAS.9.1 - PRAESUMFRQ_ACWY_M1

Table 41

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ORAL PAIN	0	0	1 (<1%)	1 (<1%)	0
POLYCYTHAEMIA VERA	0	0	1 (<1%)	1 (<1%)	0
RESPIRATORY TRACT INFECTION	0	0	1 (<1%)	1 (<1%)	0
RESTLESSNESS	0	0	1 (<1%)	1 (<1%)	0
RHINITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
RHINITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)	0
SKIN DISCOLOURATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
THIRST	0	0	1 (<1%)	1 (<1%)	0
ABDOMINAL DISTENSION	0	0	0	0	1 (<1%)
ALOPECIA	0	0	0	0	1 (<1%)
CONJUNCTIVITIS BACTERIAL	0	0	0	0	1 (<1%)
DRY MOUTH	0	0	0	0	1 (<1%)
EPISTAXIS	0	0	0	0	1 (<1%)
GASTRITIS	0	0	0	0	1 (<1%)
INFLUENZA	1 (<1%)	0	0	1 (<1%)	1 (<1%)
INJECTION SITE ANAESTHESIA	0	0	0	0	1 (<1%)
IRRITABILITY	0	0	0	0	1 (<1%)
MOTION SICKNESS	0	0	0	0	1 (<1%)
MUSCLE SPASMS	0	0	0	0	1 (<1%)
NASAL CONGESTION	1 (<1%)	0	0	1 (<1%)	1 (<1%)
OTITIS MEDIA	0	0	0	0	1 (<1%)
RASH MACULAR	0	0	0	0	1 (<1%)
RHINORRHOEA	1 (<1%)	0	0	1 (<1%)	1 (<1%)
SINUSITIS	0	0	0	0	1 (<1%)
ANOREXIA	2 (<1%)	0	0	2 (<1%)	0
AURICULAR SWELLING	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M1.SAS(WARTERO) 10JUL08, 08:55 SAS.9.1 - PRAESUMFRQ_ACWY_M1

Table 41

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
CHEST DISCOMFORT	1 (<1%)	0	0	1 (<1%)	0
DYSPNOEA	1 (<1%)	0	0	1 (<1%)	0
GINGIVAL PAIN	1 (<1%)	0	0	1 (<1%)	0
HUNGER	1 (<1%)	0	0	1 (<1%)	0
HYPOAESTHESIA	1 (<1%)	0	0	1 (<1%)	0
STOMATITIS	1 (<1%)	0	0	1 (<1%)	0
THROAT IRRITATION	1 (<1%)	0	0	1 (<1%)	0
VACCINATION COMPLICATION	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M1.SAS(WARTERO) 10JUL08, 08:55 SAS.9.1 - PRAESUMFRQ_ACWY_M1

Table 42

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6 in Descending Frequency
Comparing Total MenACWY[1] across Age Groups (Study V59P18 excluded)

MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
ABORTION SPONTANEOUS	0	1 (<1%)	0	1 (<1%)	0
HEADACHE	0	1 (<1%)	0	1 (<1%)	0
MALAISE	0	1 (<1%)	0	1 (<1%)	0
SYNOVIAL CYST	0	0	1 (<1%)	1 (<1%)	0
FACIAL PALSY	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESUMFRQ_ACWY_M26.SAS(WARTERO) 10JUL08, 08:56 SAS.9.1 - PRAESUMFRQ_ACWY_M26

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	141 (4%)	86 (8%)	130 (9%)	357 (6%)	128 (7%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	3 (<1%)	7 (<1%)	13 (<1%)	2 (<1%)
LYMPHADENOPATHY	3 (<1%)	3 (<1%)	7 (<1%)	13 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	3 (<1%)	3 (<1%)	7 (<1%)	5 (<1%)
AURICULAR SWELLING	1 (<1%)	0	0	1 (<1%)	0
EAR PAIN	0	1 (<1%)	0	1 (<1%)	1 (<1%)
MOTION SICKNESS	0	0	0	0	1 (<1%)
TINNITUS	0	0	2 (<1%)	2 (<1%)	0
VERTIGO	0	2 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
EYE DISORDERS	0	0	1 (<1%)	1 (<1%)	0
EYE SWELLING	0	0	1 (<1%)	1 (<1%)	0
GASTROINTESTINAL DISORDERS	27 (1%)	18 (2%)	9 (1%)	54 (1%)	21 (1%)
ABDOMINAL DISTENSION	0	0	0	0	1 (<1%)
ABDOMINAL PAIN	3 (<1%)	1 (<1%)	1 (<1%)	5 (<1%)	4 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	1 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)
DIARRHOEA	4 (<1%)	7 (1%)	2 (<1%)	13 (<1%)	5 (<1%)
DRY MOUTH	0	0	0	0	1 (<1%)
DYSPEPSIA	0	0	1 (<1%)	1 (<1%)	0
GASTRITIS	0	0	0	0	1 (<1%)
GINGIVAL PAIN	1 (<1%)	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
GASTROINTESTINAL DISORDERS					
NAUSEA	12 (<1%)	8 (1%)	3 (<1%)	23 (<1%)	3 (<1%)
ORAL PAIN	0	0	1 (<1%)	1 (<1%)	0
STOMACH DISCOMFORT	0	1 (<1%)	1 (<1%)	2 (<1%)	0
STOMATITIS	1 (<1%)	0	0	1 (<1%)	0
VOMITING	4 (<1%)	1 (<1%)	1 (<1%)	6 (<1%)	5 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	69 (2%)	31 (3%)	65 (4%)	165 (3%)	36 (2%)
ASTHENIA	1 (<1%)	0	0	1 (<1%)	2 (<1%)
AXILLARY PAIN	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	0
CHEST DISCOMFORT	1 (<1%)	0	0	1 (<1%)	0
CHEST PAIN	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
CHILLS	3 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	1 (<1%)
FATIGUE	1 (<1%)	2 (<1%)	6 (<1%)	9 (<1%)	2 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
HUNGER	1 (<1%)	0	0	1 (<1%)	0
INDURATION	4 (<1%)	1 (<1%)	5 (<1%)	10 (<1%)	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	2 (<1%)	3 (<1%)	0
INJECTION SITE ANAESTHESIA	0	0	0	0	1 (<1%)
INJECTION SITE BRUISING	4 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
INJECTION SITE ERYTHEMA	11 (<1%)	12 (1%)	9 (1%)	32 (1%)	2 (<1%)
INJECTION SITE HAEMORRHAGE	0	0	2 (<1%)	2 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
GEN. DISORDERS & ADMIN. SITE COND.					
INJECTION SITE INDURATION	9 (<1%)	6 (1%)	6 (<1%)	21 (<1%)	1 (<1%)
INJECTION SITE IRRITATION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE MASS	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE OEDEMA	0	1 (<1%)	1 (<1%)	2 (<1%)	0
INJECTION SITE PAIN	6 (<1%)	9 (1%)	13 (1%)	28 (<1%)	8 (<1%)
INJECTION SITE PRURITUS	10 (<1%)	3 (<1%)	12 (1%)	25 (<1%)	5 (<1%)
INJECTION SITE REACTION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE SWELLING	5 (<1%)	1 (<1%)	0	6 (<1%)	0
INJECTION SITE WARMTH	3 (<1%)	2 (<1%)	4 (<1%)	9 (<1%)	3 (<1%)
IRRITABILITY	0	0	0	0	1 (<1%)
MALAISE	12 (<1%)	8 (1%)	14 (1%)	34 (1%)	5 (<1%)
OEDEMA PERIPHERAL	0	0	1 (<1%)	1 (<1%)	0
PAIN	7 (<1%)	0	2 (<1%)	9 (<1%)	0
PYREXIA	4 (<1%)	0	2 (<1%)	6 (<1%)	0
THIRST	0	0	1 (<1%)	1 (<1%)	0
INFECTIONS & INFESTATIONS	11 (<1%)	10 (1%)	17 (1%)	38 (1%)	14 (1%)
CELLULITIS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
CONJUNCTIVITIS BACTERIAL	0	0	0	0	1 (<1%)
GASTROENTERITIS	0	1 (<1%)	2 (<1%)	3 (<1%)	0
GASTROENTERITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
INFLUENZA	1 (<1%)	0	0	1 (<1%)	1 (<1%)
INJECTION SITE INFECTION	0	0	1 (<1%)	1 (<1%)	0
NASOPHARYNGITIS	2 (<1%)	4 (<1%)	6 (<1%)	12 (<1%)	5 (<1%)
ORAL HERPES	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
OTITIS MEDIA	0	0	0	0	1 (<1%)
PHARYNGITIS	4 (<1%)	0	2 (<1%)	6 (<1%)	0
RESPIRATORY TRACT INFECTION	0	0	1 (<1%)	1 (<1%)	0
RHINITIS	1 (<1%)	0	1 (<1%)	2 (<1%)	0
SINUSITIS	0	0	0	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
VIRAL INFECTION	1 (<1%)	3 (<1%)	1 (<1%)	5 (<1%)	1 (<1%)
INJURY & POISONING	1 (<1%)	0	1 (<1%)	2 (<1%)	0
HEAT EXHAUSTION	0	0	1 (<1%)	1 (<1%)	0
VACCINATION COMPLICATION	1 (<1%)	0	0	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	0	2 (<1%)	2 (<1%)
ANOREXIA	2 (<1%)	0	0	2 (<1%)	0
INCREASED APPETITE	0	0	0	0	2 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	16 (<1%)	7 (1%)	25 (2%)	48 (1%)	21 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
MUSCULO., CONNECT. TIS. & BONE DIS.					
ARTHRALGIA	6 (<1%)	4 (<1%)	8 (1%)	18 (<1%)	11 (1%)
BACK PAIN	0	2 (<1%)	6 (<1%)	8 (<1%)	1 (<1%)
MUSCLE SPASMS	0	0	0	0	1 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
MUSCULOSKELETAL PAIN	0	0	1 (<1%)	1 (<1%)	2 (<1%)
MUSCULOSKELETAL STIFFNESS	0	0	1 (<1%)	1 (<1%)	0
MYALGIA	7 (<1%)	3 (<1%)	13 (1%)	23 (<1%)	7 (<1%)
NECK PAIN	0	0	4 (<1%)	4 (<1%)	0
PAIN IN EXTREMITY	5 (<1%)	0	1 (<1%)	6 (<1%)	3 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	0	1 (<1%)	1 (<1%)	0
POLYCYTHAEMIA VERA	0	0	1 (<1%)	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	27 (1%)	33 (3%)	30 (2%)	90 (1%)	40 (2%)
BURNING SENSATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
DIZZINESS	0	6 (1%)	4 (<1%)	10 (<1%)	12 (1%)
HEADACHE	24 (1%)	18 (2%)	20 (1%)	62 (1%)	20 (1%)
HYPOAESTHESIA	1 (<1%)	0	0	1 (<1%)	0
MIGRAINE	0	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)
MUSCLE CONTRACTIONS INVOLUNTARY	0	1 (<1%)	0	1 (<1%)	0
PARAESTHESIA	0	2 (<1%)	3 (<1%)	5 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
NERVOUS SYSTEM DISORDERS					
SINUS HEADACHE	0	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
SOMNOLENCE	1 (<1%)	2 (<1%)	2 (<1%)	5 (<1%)	2 (<1%)
SYNCOPE	1 (<1%)	0	1 (<1%)	2 (<1%)	3 (<1%)
SYNCOPE VASOVAGAL	0	2 (<1%)	0	2 (<1%)	1 (<1%)
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)	3 (<1%)	5 (<1%)	2 (<1%)
DEPRESSION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
INSOMNIA	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)
RESTLESSNESS	0	0	1 (<1%)	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
DYSMENORRHOEA	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	8 (<1%)	0	7 (<1%)	15 (<1%)	8 (<1%)
COUGH	2 (<1%)	0	0	2 (<1%)	2 (<1%)
DYSPNOEA	1 (<1%)	0	0	1 (<1%)	0
EPISTAXIS	0	0	0	0	1 (<1%)
NASAL CONGESTION	1 (<1%)	0	0	1 (<1%)	1 (<1%)
PHARYNGOLARYNGEAL PAIN	4 (<1%)	0	6 (<1%)	10 (<1%)	5 (<1%)
RHINITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)	0
RHINORRHOEA	1 (<1%)	0	0	1 (<1%)	1 (<1%)
THROAT IRRITATION	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 43

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SKIN & SUBCUTANEOUS TIS. DISORDERS	9 (<1%)	6 (1%)	16 (1%)	31 (1%)	16 (1%)
ALOPECIA	0	0	0	0	1 (<1%)
DERMATITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)	0
ECCHYMOSIS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
ERYTHEMA	5 (<1%)	1 (<1%)	8 (1%)	14 (<1%)	4 (<1%)
HYPERHIDROSIS	0	0	2 (<1%)	2 (<1%)	2 (<1%)
PRURITUS	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
RASH	3 (<1%)	4 (<1%)	6 (<1%)	13 (<1%)	5 (<1%)
RASH MACULAR	0	0	0	0	1 (<1%)
SKIN DISCOLOURATION	0	0	1 (<1%)	1 (<1%)	1 (<1%)
URTICARIA	0	0	2 (<1%)	2 (<1%)	0
VASCULAR DISORDERS	0	0	2 (<1%)	2 (<1%)	2 (<1%)
FLUSHING	0	0	2 (<1%)	2 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - PRAESUM_ACWY_M1

Table 44.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	110 (4%)	31 (3%)	141 (4%)	33 (6%)	4 (2%)	28 (3%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
LYMPHADENOPATHY	3 (<1%)	0	3 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
AURICULAR SWELLING	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	21 (1%)	6 (1%)	27 (1%)	6 (1%)	0	8 (1%)
ABDOMINAL PAIN	1 (<1%)	2 (<1%)	3 (<1%)	0	0	1 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
DIARRHOEA	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	0	0
GINGIVAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
NAUSEA	10 (<1%)	2 (<1%)	12 (<1%)	1 (<1%)	0	4 (<1%)
ODYNOPHAGIA	0	0	0	0	0	1 (<1%)
STOMATITIS	1 (<1%)	0	1 (<1%)	0	0	0
VOMITING	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	58 (2%)	11 (1%)	69 (2%)	10 (2%)	2 (1%)	12 (1%)
ASTHENIA	1 (<1%)	0	1 (<1%)	0	0	0
AXILLARY PAIN	1 (<1%)	0	1 (<1%)	0	0	0
CHEST DISCOMFORT	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
GEN. DISORDERS & ADMIN. SITE COND.						
CHEST PAIN	1 (<1%)	0	1 (<1%)	0	0	0
CHILLS	3 (<1%)	0	3 (<1%)	0	0	2 (<1%)
FATIGUE	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
FEELING HOT	1 (<1%)	0	1 (<1%)	0	0	0
HUNGER	1 (<1%)	0	1 (<1%)	0	0	0
INDURATION	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	0	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE ANAESTHESIA	0	0	0	1 (<1%)	0	0
INJECTION SITE BRUISING	4 (<1%)	0	4 (<1%)	1 (<1%)	1 (<1%)	0
INJECTION SITE ERYTHEMA	10 (<1%)	1 (<1%)	11 (<1%)	1 (<1%)	0	1 (<1%)
INJECTION SITE INDURATION	7 (<1%)	2 (<1%)	9 (<1%)	0	0	2 (<1%)
INJECTION SITE PAIN	6 (<1%)	0	6 (<1%)	2 (<1%)	0	1 (<1%)
INJECTION SITE PRURITUS	10 (<1%)	0	10 (<1%)	1 (<1%)	0	0
INJECTION SITE SWELLING	5 (<1%)	0	5 (<1%)	0	0	1 (<1%)
INJECTION SITE WARMTH	3 (<1%)	0	3 (<1%)	0	0	0
IRRITABILITY	0	0	0	1 (<1%)	0	0
MALAISE	9 (<1%)	3 (<1%)	12 (<1%)	2 (<1%)	1 (<1%)	6 (1%)
PAIN	4 (<1%)	3 (<1%)	7 (<1%)	0	0	1 (<1%)
PYREXIA	1 (<1%)	3 (<1%)	4 (<1%)	0	0	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
INFECTIONS & INFESTATIONS	6 (<1%)	5 (1%)	11 (<1%)	2 (<1%)	0	0
CELLULITIS	0	1 (<1%)	1 (<1%)	0	0	0
INFLUENZA	1 (<1%)	0	1 (<1%)	0	0	0
NASOPHARYNGITIS	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
PHARYNGITIS	3 (<1%)	1 (<1%)	4 (<1%)	0	0	0
RHINITIS	0	1 (<1%)	1 (<1%)	0	0	0
UPPER RESPIRATORY TRACT INFECTION	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0
VIRAL INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
INJURY & POISONING	1 (<1%)	0	1 (<1%)	0	0	0
VACCINATION COMPLICATION	1 (<1%)	0	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	2 (<1%)	0	0	0
ANOREXIA	2 (<1%)	0	2 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	13 (<1%)	3 (<1%)	16 (<1%)	5 (1%)	3 (1%)	6 (1%)
ARTHRALGIA	5 (<1%)	1 (<1%)	6 (<1%)	2 (<1%)	0	2 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
MUSCULOSKELETAL PAIN	0	0	0	1 (<1%)	0	0
MYALGIA	7 (<1%)	0	7 (<1%)	2 (<1%)	1 (<1%)	5 (1%)
NECK PAIN	0	0	0	0	1 (<1%)	0
PAIN IN EXTREMITY	3 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
NERVOUS SYSTEM DISORDERS	16 (1%)	11 (1%)	27 (1%)	10 (2%)	0	13 (1%)
BURNING SENSATION	0	0	0	0	0	1 (<1%)
DIZZINESS	0	0	0	2 (<1%)	0	1 (<1%)
HEADACHE	13 (<1%)	11 (1%)	24 (1%)	3 (1%)	0	11 (1%)
HYPOAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0
MIGRAINE	0	0	0	1 (<1%)	0	0
SOMNOLENCE	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
SYNCOPE	1 (<1%)	0	1 (<1%)	3 (1%)	0	0
SYNCOPE VASOVAGAL	0	0	0	1 (<1%)	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
INSOMNIA	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
REPRODUCT. SYS. & BREAST DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
DYSMENORRHOEA	0	1 (<1%)	1 (<1%)	0	0	0
RESP., THORACIC & MEDIASTINAL DIS.	8 (<1%)	0	8 (<1%)	3 (1%)	0	1 (<1%)
ASTHMA	0	0	0	0	0	1 (<1%)
COUGH	2 (<1%)	0	2 (<1%)	0	0	0
DYSPNOEA	1 (<1%)	0	1 (<1%)	0	0	0
NASAL CONGESTION	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
PHARYNGOLARYNGEAL PAIN	4 (<1%)	0	4 (<1%)	2 (<1%)	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
RESP., THORACIC & MEDIASTINAL DIS.						
RHINORRHOEA	1 (<1%)	0	1 (<1%)	0	0	0
THROAT IRRITATION	1 (<1%)	0	1 (<1%)	0	0	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	7 (<1%)	2 (<1%)	9 (<1%)	6 (1%)	0	2 (<1%)
ALOPECIA	0	0	0	1 (<1%)	0	0
ERYTHEMA	3 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)	0	0
PRURITUS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
RASH	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
RASH PRURITIC	0	0	0	0	0	2 (<1%)
SKIN DISCOLOURATION	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	86 (8%)	38 (7%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	2 (<1%)
LYMPHADENOPATHY	3 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	3 (<1%)	2 (<1%)
EAR PAIN	1 (<1%)	0
MOTION SICKNESS	0	1 (<1%)
VERTIGO	2 (<1%)	1 (<1%)
GASTROINTESTINAL DISORDERS	18 (2%)	9 (2%)
ABDOMINAL PAIN	1 (<1%)	3 (1%)
ABDOMINAL PAIN UPPER	1 (<1%)	0
DIARRHOEA	7 (1%)	1 (<1%)
DRY MOUTH	0	1 (<1%)
GASTRITIS	0	1 (<1%)
NAUSEA	8 (1%)	2 (<1%)
STOMACH DISCOMFORT	1 (<1%)	0
VOMITING	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	31 (3%)	8 (1%)
ASTHENIA	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
AXILLARY PAIN	1 (<1%)	0
CHEST PAIN	1 (<1%)	0
CHILLS	1 (<1%)	0
FATIGUE	2 (<1%)	0
FEELING HOT	1 (<1%)	0
INDURATION	1 (<1%)	1 (<1%)
INJECTION SITE BRUISING	1 (<1%)	0
INJECTION SITE ERYTHEMA	12 (1%)	0
INJECTION SITE INDURATION	6 (1%)	1 (<1%)
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	9 (1%)	1 (<1%)
INJECTION SITE PRURITUS	3 (<1%)	3 (1%)
INJECTION SITE SWELLING	1 (<1%)	0
INJECTION SITE WARMTH	2 (<1%)	0
MALAISE	8 (1%)	1 (<1%)
INFECTIONS & INFESTATIONS	10 (1%)	6 (1%)
CELLULITIS	1 (<1%)	0
CONJUNCTIVITIS BACTERIAL	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

Table 44.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
INFECTIONS & INFESTATIONS		
GASTROENTERITIS	1 (<1%)	0
INFLUENZA	0	1 (<1%)
NASOPHARYNGITIS	4 (<1%)	2 (<1%)
ORAL HERPES	1 (<1%)	0
OTITIS MEDIA	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)
VIRAL INFECTION	3 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
INCREASED APPETITE	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	7 (1%)	5 (1%)
ARTHRALGIA	4 (<1%)	2 (<1%)
BACK PAIN	2 (<1%)	1 (<1%)
MUSCLE SPASMS	0	1 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	0
MYALGIA	3 (<1%)	2 (<1%)
NERVOUS SYSTEM DISORDERS	33 (3%)	10 (2%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
DIZZINESS	6 (1%)	2 (<1%)
HEADACHE	18 (2%)	7 (1%)
MIGRAINE	3 (<1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	1 (<1%)	0
PARAESTHESIA	2 (<1%)	1 (<1%)
SINUS HEADACHE	1 (<1%)	0
SOMNOLENCE	2 (<1%)	0
SYNCOPE VASOVAGAL	2 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)
DEPRESSION	0	1 (<1%)
INSOMNIA	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	0
DYSMENORRHOEA	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
SKIN & SUBCUTANEOUS TIS. DISORDERS	6 (1%)	3 (1%)
ECCHYMOSIS	1 (<1%)	0
ERYTHEMA	1 (<1%)	2 (<1%)
PRURITUS	1 (<1%)	0
RASH	4 (<1%)	0
RASH MACULAR	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	130 (9%)	57 (9%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	7 (<1%)	0
LYMPHADENOPATHY	7 (<1%)	0
EAR & LABYRINTH DISORDERS	3 (<1%)	3 (<1%)
EAR PAIN	0	1 (<1%)
TINNITUS	2 (<1%)	0
VERTIGO	1 (<1%)	2 (<1%)
EYE DISORDERS	1 (<1%)	0
EYE SWELLING	1 (<1%)	0
GASTROINTESTINAL DISORDERS	9 (1%)	6 (1%)
ABDOMINAL DISTENSION	0	1 (<1%)
ABDOMINAL PAIN	1 (<1%)	1 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	0
DIARRHOEA	2 (<1%)	2 (<1%)
DYSPEPSIA	1 (<1%)	0
NAUSEA	3 (<1%)	0
ORAL PAIN	1 (<1%)	0
STOMACH DISCOMFORT	1 (<1%)	0
VOMITING	1 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
GEN. DISORDERS & ADMIN. SITE COND.	65 (4%)	18 (3%)
ASTHENIA	0	1 (<1%)
AXILLARY PAIN	2 (<1%)	0
CHEST PAIN	1 (<1%)	0
CHILLS	4 (<1%)	1 (<1%)
FATIGUE	6 (<1%)	1 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)
INDURATION	5 (<1%)	0
INFLUENZA LIKE ILLNESS	2 (<1%)	0
INJECTION SITE BRUISING	0	1 (<1%)
INJECTION SITE ERYTHEMA	9 (1%)	1 (<1%)
INJECTION SITE HAEMORRHAGE	2 (<1%)	1 (<1%)
INJECTION SITE INDURATION	6 (<1%)	0
INJECTION SITE IRRITATION	1 (<1%)	0
INJECTION SITE MASS	1 (<1%)	0
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	13 (1%)	5 (1%)
INJECTION SITE PRURITUS	12 (1%)	1 (<1%)
INJECTION SITE REACTION	1 (<1%)	0
INJECTION SITE WARMTH	4 (<1%)	3 (<1%)
MALAISE	14 (1%)	2 (<1%)
OEDEMA PERIPHERAL	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
PAIN	2 (<1%)	0
PYREXIA	2 (<1%)	0
THIRST	1 (<1%)	0
INFECTIONS & INFESTATIONS	17 (1%)	6 (1%)
GASTROENTERITIS	2 (<1%)	0
GASTROENTERITIS VIRAL	1 (<1%)	0
INJECTION SITE INFECTION	1 (<1%)	0
NASOPHARYNGITIS	6 (<1%)	2 (<1%)
ORAL HERPES	1 (<1%)	1 (<1%)
PHARYNGITIS	2 (<1%)	0
RESPIRATORY TRACT INFECTION	1 (<1%)	0
RHINITIS	1 (<1%)	0
SINUSITIS	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)
VIRAL INFECTION	1 (<1%)	1 (<1%)
INJURY & POISONING	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
METABOLISM & NUTRITION DISORDERS		
INCREASED APPETITE	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	25 (2%)	11 (2%)
ARTHRALGIA	8 (1%)	7 (1%)
BACK PAIN	6 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	1 (<1%)
MUSCULOSKELETAL STIFFNESS	1 (<1%)	0
MYALGIA	13 (1%)	3 (<1%)
NECK PAIN	4 (<1%)	0
PAIN IN EXTREMITY	1 (<1%)	2 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0
POLYCYTHAEMIA VERA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	30 (2%)	20 (3%)
BURNING SENSATION	1 (<1%)	1 (<1%)
DIZZINESS	4 (<1%)	8 (1%)
HEADACHE	20 (1%)	10 (2%)
MIGRAINE	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
PARAESTHESIA	3 (<1%)	0
SINUS HEADACHE	1 (<1%)	1 (<1%)
SOMNOLENCE	2 (<1%)	2 (<1%)
SYNCOPE	1 (<1%)	0
PSYCHIATRIC DISORDERS	3 (<1%)	0
DEPRESSION	1 (<1%)	0
INSOMNIA	2 (<1%)	0
RESTLESSNESS	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	7 (<1%)	4 (1%)
COUGH	0	2 (<1%)
EPISTAXIS	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	6 (<1%)	2 (<1%)
RHINITIS ALLERGIC	1 (<1%)	0
RHINORRHOEA	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	16 (1%)	7 (1%)
DERMATITIS ALLERGIC	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 44.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
ECCHYMOSIS	0	1 (<1%)
ERYTHEMA	8 (1%)	1 (<1%)
HYPERHIDROSIS	2 (<1%)	2 (<1%)
RASH	6 (<1%)	3 (<1%)
SKIN DISCOLOURATION	1 (<1%)	0
URTICARIA	2 (<1%)	0
VASCULAR DISORDERS	2 (<1%)	2 (<1%)
FLUSHING	2 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	106 (4%)	29 (3%)	135 (4%)	32 (6%)	4 (2%)	23 (3%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
LYMPHADENOPATHY	3 (<1%)	0	3 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
AURICULAR SWELLING	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	20 (1%)	6 (1%)	26 (1%)	6 (1%)	0	7 (1%)
ABDOMINAL PAIN	1 (<1%)	2 (<1%)	3 (<1%)	0	0	1 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
DIARRHOEA	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	0	0
GINGIVAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
NAUSEA	9 (<1%)	2 (<1%)	11 (<1%)	1 (<1%)	0	4 (<1%)
ODYNOPHAGIA	0	0	0	0	0	1 (<1%)
STOMATITIS	1 (<1%)	0	1 (<1%)	0	0	0
VOMITING	3 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)	0	0
GEN. DISORDERS & ADMIN. SITE COND.	54 (2%)	11 (1%)	65 (2%)	10 (2%)	2 (1%)	11 (1%)
ASTHENIA	1 (<1%)	0	1 (<1%)	0	0	0
AXILLARY PAIN	1 (<1%)	0	1 (<1%)	0	0	0
CHEST DISCOMFORT	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
GEN. DISORDERS & ADMIN. SITE COND.						
CHEST PAIN	1 (<1%)	0	1 (<1%)	0	0	0
CHILLS	3 (<1%)	0	3 (<1%)	0	0	2 (<1%)
FATIGUE	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
FEELING HOT	1 (<1%)	0	1 (<1%)	0	0	0
HUNGER	1 (<1%)	0	1 (<1%)	0	0	0
INDURATION	3 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	0	2 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE ANAESTHESIA	0	0	0	1 (<1%)	0	0
INJECTION SITE BRUISING	4 (<1%)	0	4 (<1%)	1 (<1%)	1 (<1%)	0
INJECTION SITE ERYTHEMA	9 (<1%)	1 (<1%)	10 (<1%)	1 (<1%)	0	1 (<1%)
INJECTION SITE INDURATION	7 (<1%)	2 (<1%)	9 (<1%)	0	0	2 (<1%)
INJECTION SITE PAIN	5 (<1%)	0	5 (<1%)	2 (<1%)	0	1 (<1%)
INJECTION SITE PRURITUS	10 (<1%)	0	10 (<1%)	1 (<1%)	0	0
INJECTION SITE SWELLING	5 (<1%)	0	5 (<1%)	0	0	1 (<1%)
INJECTION SITE WARMTH	3 (<1%)	0	3 (<1%)	0	0	0
IRRITABILITY	0	0	0	1 (<1%)	0	0
MALAISE	9 (<1%)	3 (<1%)	12 (<1%)	2 (<1%)	1 (<1%)	5 (1%)
PAIN	3 (<1%)	3 (<1%)	6 (<1%)	0	0	1 (<1%)
PYREXIA	0	3 (<1%)	3 (<1%)	0	0	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
INFECTIONS & INFESTATIONS	6 (<1%)	5 (1%)	11 (<1%)	2 (<1%)	0	0
CELLULITIS	0	1 (<1%)	1 (<1%)	0	0	0
INFLUENZA	1 (<1%)	0	1 (<1%)	0	0	0
NASOPHARYNGITIS	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
PHARYNGITIS	3 (<1%)	1 (<1%)	4 (<1%)	0	0	0
RHINITIS	0	1 (<1%)	1 (<1%)	0	0	0
UPPER RESPIRATORY TRACT INFECTION	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0
VIRAL INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
INJURY & POISONING	1 (<1%)	0	1 (<1%)	0	0	0
VACCINATION COMPLICATION	1 (<1%)	0	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	2 (<1%)	0	0	0
ANOREXIA	2 (<1%)	0	2 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	13 (<1%)	3 (<1%)	16 (<1%)	5 (1%)	3 (1%)	4 (<1%)
ARTHRALGIA	5 (<1%)	1 (<1%)	6 (<1%)	2 (<1%)	0	1 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
MUSCULOSKELETAL PAIN	0	0	0	1 (<1%)	0	0
MYALGIA	7 (<1%)	0	7 (<1%)	2 (<1%)	1 (<1%)	4 (<1%)
NECK PAIN	0	0	0	0	1 (<1%)	0
PAIN IN EXTREMITY	3 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
NERVOUS SYSTEM DISORDERS	15 (1%)	10 (1%)	25 (1%)	10 (2%)	0	11 (1%)
BURNING SENSATION	0	0	0	0	0	1 (<1%)
DIZZINESS	0	0	0	2 (<1%)	0	0
HEADACHE	12 (<1%)	10 (1%)	22 (1%)	3 (1%)	0	9 (1%)
HYPOAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0
MIGRAINE	0	0	0	1 (<1%)	0	0
SOMNOLENCE	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
SYNCOPE	1 (<1%)	0	1 (<1%)	3 (1%)	0	0
SYNCOPE VASOVAGAL	0	0	0	1 (<1%)	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
INSOMNIA	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
RESP., THORACIC & MEDIASTINAL DIS.	8 (<1%)	0	8 (<1%)	3 (1%)	0	1 (<1%)
ASTHMA	0	0	0	0	0	1 (<1%)
COUGH	2 (<1%)	0	2 (<1%)	0	0	0
DYSPNOEA	1 (<1%)	0	1 (<1%)	0	0	0
NASAL CONGESTION	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
PHARYNGOLARYNGEAL PAIN	4 (<1%)	0	4 (<1%)	2 (<1%)	0	0
RHINORRHOEA	1 (<1%)	0	1 (<1%)	0	0	0
THROAT IRRITATION	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
SKIN & SUBCUTANEOUS TIS. DISORDERS	7 (<1%)	2 (<1%)	9 (<1%)	5 (1%)	0	2 (<1%)
ERYTHEMA	3 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)	0	0
PRURITUS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
RASH	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
RASH PRURITIC	0	0	0	0	0	2 (<1%)
SKIN DISCOLOURATION	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	84 (7%)	36 (6%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	1 (<1%)
LYMPHADENOPATHY	3 (<1%)	1 (<1%)
EAR & LABYRINTH DISORDERS	3 (<1%)	2 (<1%)
EAR PAIN	1 (<1%)	0
MOTION SICKNESS	0	1 (<1%)
VERTIGO	2 (<1%)	1 (<1%)
GASTROINTESTINAL DISORDERS	18 (2%)	9 (2%)
ABDOMINAL PAIN	1 (<1%)	3 (1%)
ABDOMINAL PAIN UPPER	1 (<1%)	0
DIARRHOEA	7 (1%)	1 (<1%)
DRY MOUTH	0	1 (<1%)
GASTRITIS	0	1 (<1%)
NAUSEA	8 (1%)	2 (<1%)
STOMACH DISCOMFORT	1 (<1%)	0
VOMITING	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	31 (3%)	8 (1%)
ASTHENIA	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
AXILLARY PAIN	1 (<1%)	0
CHEST PAIN	1 (<1%)	0
CHILLS	1 (<1%)	0
FATIGUE	2 (<1%)	0
FEELING HOT	1 (<1%)	0
INDURATION	1 (<1%)	1 (<1%)
INJECTION SITE BRUISING	1 (<1%)	0
INJECTION SITE ERYTHEMA	12 (1%)	0
INJECTION SITE INDURATION	6 (1%)	1 (<1%)
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	9 (1%)	1 (<1%)
INJECTION SITE PRURITUS	3 (<1%)	3 (1%)
INJECTION SITE SWELLING	1 (<1%)	0
INJECTION SITE WARMTH	2 (<1%)	0
MALAISE	8 (1%)	1 (<1%)
INFECTIONS & INFESTATIONS	10 (1%)	5 (1%)
CELLULITIS	1 (<1%)	0
CONJUNCTIVITIS BACTERIAL	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

Table 45.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
INFECTIONS & INFESTATIONS		
GASTROENTERITIS	1 (<1%)	0
INFLUENZA	0	1 (<1%)
NASOPHARYNGITIS	4 (<1%)	2 (<1%)
ORAL HERPES	1 (<1%)	0
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)
VIRAL INFECTION	3 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
INCREASED APPETITE	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	7 (1%)	5 (1%)
ARTHRALGIA	4 (<1%)	2 (<1%)
BACK PAIN	2 (<1%)	1 (<1%)
MUSCLE SPASMS	0	1 (<1%)
MUSCULAR WEAKNESS	1 (<1%)	0
MYALGIA	3 (<1%)	2 (<1%)
NERVOUS SYSTEM DISORDERS	32 (3%)	10 (2%)
DIZZINESS	6 (1%)	2 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
NERVOUS SYSTEM DISORDERS		
HEADACHE	17 (1%)	7 (1%)
MIGRAINE	3 (<1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	1 (<1%)	0
PARAESTHESIA	2 (<1%)	1 (<1%)
SINUS HEADACHE	1 (<1%)	0
SOMNOLENCE	2 (<1%)	0
SYNCOPE VASOVAGAL	2 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)
DEPRESSION	0	1 (<1%)
INSOMNIA	1 (<1%)	0
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	0
DYSMENORRHOEA	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	5 (<1%)	3 (1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
ECCHYMOSIS	1 (<1%)	0
ERYTHEMA	1 (<1%)	2 (<1%)
PRURITUS	1 (<1%)	0
RASH	3 (<1%)	0
RASH MACULAR	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	126 (9%)	55 (8%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	7 (<1%)	0
LYMPHADENOPATHY	7 (<1%)	0
EAR & LABYRINTH DISORDERS	3 (<1%)	2 (<1%)
EAR PAIN	0	1 (<1%)
TINNITUS	2 (<1%)	0
VERTIGO	1 (<1%)	1 (<1%)
EYE DISORDERS	1 (<1%)	0
EYE SWELLING	1 (<1%)	0
GASTROINTESTINAL DISORDERS	9 (1%)	6 (1%)
ABDOMINAL DISTENSION	0	1 (<1%)
ABDOMINAL PAIN	1 (<1%)	1 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	0
DIARRHOEA	2 (<1%)	2 (<1%)
DYSPEPSIA	1 (<1%)	0
NAUSEA	3 (<1%)	0
ORAL PAIN	1 (<1%)	0
STOMACH DISCOMFORT	1 (<1%)	0
VOMITING	1 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_D17_35_55.SAS(WARTERO) 10JUL08, 08:26 SAS.9.1 - PRAESUM_TRT_D17_35_55

Table 45.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
GEN. DISORDERS & ADMIN. SITE COND.	60 (4%)	17 (3%)
ASTHENIA	0	1 (<1%)
AXILLARY PAIN	2 (<1%)	0
CHEST PAIN	1 (<1%)	0
CHILLS	3 (<1%)	1 (<1%)
FATIGUE	6 (<1%)	1 (<1%)
FEELING HOT	1 (<1%)	1 (<1%)
INDURATION	5 (<1%)	0
INFLUENZA LIKE ILLNESS	2 (<1%)	0
INJECTION SITE BRUISING	0	1 (<1%)
INJECTION SITE ERYTHEMA	8 (1%)	1 (<1%)
INJECTION SITE HAEMORRHAGE	2 (<1%)	1 (<1%)
INJECTION SITE INDURATION	6 (<1%)	0
INJECTION SITE IRRITATION	1 (<1%)	0
INJECTION SITE MASS	1 (<1%)	0
INJECTION SITE OEDEMA	1 (<1%)	0
INJECTION SITE PAIN	13 (1%)	4 (1%)
INJECTION SITE PRURITUS	11 (1%)	1 (<1%)
INJECTION SITE REACTION	1 (<1%)	0
INJECTION SITE WARMTH	4 (<1%)	3 (<1%)
MALAISE	11 (1%)	2 (<1%)
OEDEMA PERIPHERAL	1 (<1%)	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
GEN. DISORDERS & ADMIN. SITE COND.		
PAIN	2 (<1%)	0
PYREXIA	2 (<1%)	0
THIRST	1 (<1%)	0
INFECTIONS & INFESTATIONS	16 (1%)	6 (1%)
GASTROENTERITIS	2 (<1%)	0
GASTROENTERITIS VIRAL	1 (<1%)	0
INJECTION SITE INFECTION	1 (<1%)	0
NASOPHARYNGITIS	6 (<1%)	2 (<1%)
ORAL HERPES	1 (<1%)	1 (<1%)
PHARYNGITIS	2 (<1%)	0
RESPIRATORY TRACT INFECTION	1 (<1%)	0
SINUSITIS	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	1 (<1%)
VIRAL INFECTION	1 (<1%)	1 (<1%)
INJURY & POISONING	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
INCREASED APPETITE	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 45.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
MUSCULO., CONNECT. TIS. & BONE DIS.	21 (1%)	11 (2%)
ARTHRALGIA	7 (<1%)	7 (1%)
BACK PAIN	5 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	1 (<1%)
MUSCULOSKELETAL STIFFNESS	1 (<1%)	0
MYALGIA	10 (1%)	3 (<1%)
NECK PAIN	4 (<1%)	0
PAIN IN EXTREMITY	1 (<1%)	2 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0
POLYCYTHAEMIA VERA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	28 (2%)	19 (3%)
BURNING SENSATION	1 (<1%)	1 (<1%)
DIZZINESS	2 (<1%)	7 (1%)
HEADACHE	19 (1%)	9 (1%)
MIGRAINE	1 (<1%)	0
PARAESTHESIA	3 (<1%)	0
SINUS HEADACHE	1 (<1%)	1 (<1%)
SOMNOLENCE	2 (<1%)	2 (<1%)
SYNCOPE	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_D17_35_55.SAS(WARTERO) 10JUL08, 08:26 SAS.9.1 - PRAESUM_TRT_D17_35_55

Table 45.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 1 to 7, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
PSYCHIATRIC DISORDERS	3 (<1%)	0
DEPRESSION	1 (<1%)	0
INSOMNIA	2 (<1%)	0
RESTLESSNESS	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	7 (<1%)	4 (1%)
COUGH	0	2 (<1%)
EPISTAXIS	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	6 (<1%)	2 (<1%)
RHINITIS ALLERGIC	1 (<1%)	0
RHINORRHOEA	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	16 (1%)	7 (1%)
DERMATITIS ALLERGIC	1 (<1%)	0
ECCHYMOSIS	0	1 (<1%)
ERYTHEMA	8 (1%)	1 (<1%)
HYPERHIDROSIS	2 (<1%)	2 (<1%)
RASH	6 (<1%)	3 (<1%)
URTICARIA	2 (<1%)	0
VASCULAR DISORDERS	2 (<1%)	2 (<1%)
FLUSHING	2 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 46.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 8 to 29, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	4 (<1%)	3 (<1%)	7 (<1%)	1 (<1%)	0	5 (1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	1 (<1%)	2 (<1%)	0	0	1 (<1%)
NAUSEA	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
VOMITING	0	0	0	0	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	4 (<1%)	0	4 (<1%)	0	0	1 (<1%)
INJECTION SITE ERYTHEMA	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE PAIN	1 (<1%)	0	1 (<1%)	0	0	0
MALAISE	0	0	0	0	0	1 (<1%)
PAIN	1 (<1%)	0	1 (<1%)	0	0	0
PYREXIA	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	0	0	0	0	2 (<1%)
ARTHRALGIA	0	0	0	0	0	1 (<1%)
MYALGIA	0	0	0	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)	2 (<1%)	0	0	2 (<1%)
DIZZINESS	0	0	0	0	0	1 (<1%)
HEADACHE	1 (<1%)	1 (<1%)	2 (<1%)	0	0	2 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
DYSMENORRHOEA	0	1 (<1%)	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_D829_11_18.SAS(WARTERO) 10JUL08, 08:27 SAS.9.1 - PRAESUM_TRT_D829_11_18

Table 46.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 8 to 29, Comparing Treatment within Age Groups
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	1 (<1%)	0	0
ALOPECIA	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 46.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 8 to 29, Comparing Treatment within Age Groups
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	3 (<1%)	3 (1%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	0	1 (<1%)
LYMPHADENOPATHY	0	1 (<1%)
INFECTIONS & INFESTATIONS	0	1 (<1%)
OTITIS MEDIA	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)
HEADACHE	1 (<1%)	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	2 (<1%)	0
RASH	2 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 46.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 8 to 29, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	10 (1%)	4 (1%)
EAR & LABYRINTH DISORDERS	0	1 (<1%)
VERTIGO	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	5 (<1%)	1 (<1%)
CHILLS	1 (<1%)	0
INJECTION SITE ERYTHEMA	1 (<1%)	0
INJECTION SITE PAIN	0	1 (<1%)
INJECTION SITE PRURITUS	1 (<1%)	0
MALAISE	3 (<1%)	0
INFECTIONS & INFESTATIONS	1 (<1%)	0
RHINITIS	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	5 (<1%)	0
ARTHRALGIA	1 (<1%)	0
BACK PAIN	1 (<1%)	0
MYALGIA	3 (<1%)	0
NERVOUS SYSTEM DISORDERS	3 (<1%)	2 (<1%)
DIZZINESS	2 (<1%)	1 (<1%)
HEADACHE	1 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 46.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Days 8 to 29, Comparing Treatment within Age Groups
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0
SKIN DISCOLOURATION	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
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Table 47

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
ANY ADVERSE EVENT	0	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	1 (<1%)	0	1 (<1%)	0
MALAISE	0	1 (<1%)	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	0	1 (<1%)	1 (<1%)	0
SYNOVIAL CYST	0	0	1 (<1%)	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
FACIAL PALSY	0	0	0	0	1 (<1%)
HEADACHE	0	1 (<1%)	0	1 (<1%)	0
PREG., PUERPERIUM & PERINATAL COND.	0	1 (<1%)	0	1 (<1%)	0
ABORTION SPONTANEOUS	0	1 (<1%)	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - PRAESUM_ACWY_M26

Table 48.1

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
ANY ADVERSE EVENT	0	0	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	0	1 (<1%)	0
ERYTHEMA	0	0	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - PRAESUM_TRT_M26_11_18

Agent: MenACWY

Table 48.2

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	2 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	1 (<1%)	0
MALAISE	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)
FACIAL PALSY	0	1 (<1%)
HEADACHE	1 (<1%)	0
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	0
ABORTION SPONTANEOUS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - PRAESUM_TRT_M26_19_34

Table 48.3

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0
SYNOVIAL CYST	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1 - PRAESUM_TRT_M26_35_55

Table 49

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	7 (<1%)	5 (<1%)	9 (1%)	21 (<1%)	5 (<1%)
GASTROINTESTINAL DISORDERS	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	0
NAUSEA	2 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	2 (<1%)	3 (<1%)	5 (<1%)	10 (<1%)	0
AXILLARY PAIN	0	0	1 (<1%)	1 (<1%)	0
CHILLS	1 (<1%)	0	0	1 (<1%)	0
INDURATION	0	0	1 (<1%)	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
MALAISE	0	2 (<1%)	3 (<1%)	5 (<1%)	0
OEDEMA PERIPHERAL	0	0	1 (<1%)	1 (<1%)	0
INFECTIONS & INFESTATIONS	1 (<1%)	0	0	1 (<1%)	0
CELLULITIS	1 (<1%)	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	2 (<1%)	0	2 (<1%)	4 (<1%)	1 (<1%)
ARTHRALGIA	0	0	2 (<1%)	2 (<1%)	1 (<1%)
MYALGIA	2 (<1%)	0	1 (<1%)	3 (<1%)	0
NERVOUS SYSTEM DISORDERS	3 (<1%)	2 (<1%)	4 (<1%)	9 (<1%)	4 (<1%)
HEADACHE	3 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	3 (<1%)
MIGRAINE	0	0	0	0	1 (<1%)
SYNCOPE VASOVAGAL	0	1 (<1%)	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - PRAESUM_SEV_ACWY_M1

Table 49

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
PSYCHIATRIC DISORDERS					
DEPRESSION	0	0	1 (<1%)	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	2 (<1%)	2 (<1%)	0
ERYTHEMA	0	0	1 (<1%)	1 (<1%)	0
RASH	0	0	1 (<1%)	1 (<1%)	0
URTICARIA	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M1.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - PRAESUM_SEV_ACWY_M1

Table 50.1

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	5 (<1%)	2 (<1%)	7 (<1%)	1 (<1%)	0	2 (<1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
NAUSEA	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
GEN. DISORDERS & ADMIN. SITE COND.	2 (<1%)	0	2 (<1%)	0	0	0
CHILLS	1 (<1%)	0	1 (<1%)	0	0	0
INJECTION SITE PAIN	1 (<1%)	0	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	0	1 (<1%)	1 (<1%)	0	0	0
CELLULITIS	0	1 (<1%)	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)
MYALGIA	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)
DIZZINESS	0	0	0	0	0	1 (<1%)
HEADACHE	2 (<1%)	1 (<1%)	3 (<1%)	0	0	1 (<1%)
MIGRAINE	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_11_18.SAS(WARTERO) 10JUL08, 08:17 SAS.9.1 - PRAESUM_SEV_TRT_M1_11_18

Table 50.2

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	5 (<1%)	1 (<1%)
GASTROINTESTINAL DISORDERS	2 (<1%)	0
NAUSEA	2 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	3 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0
MALAISE	2 (<1%)	0
NERVOUS SYSTEM DISORDERS	2 (<1%)	1 (<1%)
HEADACHE	1 (<1%)	1 (<1%)
SYNCOPE VASOVAGAL	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_19_34.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - PRAESUM_SEV_TRT_M1_19_34

Table 50.3

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	9 (1%)	3 (<1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	0
NAUSEA	1 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	5 (<1%)	0
AXILLARY PAIN	1 (<1%)	0
INDURATION	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0
MALAISE	3 (<1%)	0
OEDEMA PERIPHERAL	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	2 (<1%)	1 (<1%)
ARTHRALGIA	2 (<1%)	1 (<1%)
MYALGIA	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	4 (<1%)	2 (<1%)
HEADACHE	4 (<1%)	2 (<1%)
PSYCHIATRIC DISORDERS	1 (<1%)	0
DEPRESSION	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_35_55.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - PRAESUM_SEV_TRT_M1_35_55

Table 50.3

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
ERYTHEMA	1 (<1%)	0
RASH	1 (<1%)	0
URTICARIA	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M1_35_55.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - PRAESUM_SEV_TRT_M1_35_55

Table 51

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_ACWY_M26.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - PRAESUM_SEV_ACWY_M26

Table 52.1

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:18 SAS.9.1 - PRAESUM_SEV_TRT_M26_11_18

Table 52.2

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - PRAESUM_SEV_TRT_M26_19_34

Table 52.3

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:19 SAS.9.1 - PRAESUM_SEV_TRT_M26_35_55

Table 53

Summary of Demographic Characteristics, Comparing Across Geographic Regions
US vs Latin America, Ages 19-55

	P13 ACWY (N=1018)	P13 Menact (N=336)	P17 ACWY (N=1588)	P17 Menact (N=882)
Age (Years):				
Mean	38.9	38.7	34.6	34.8
Median	40.0	40.0	33.0	34.0
Std. Dev.	9.6	9.9	10.1	10.4
Min	19	19	19	19
Max	55	55	55	55
N	1018	336	1588	882
Sex:				
MALE	248 (24%)	84 (25%)	508 (32%)	271 (31%)
FEMALE	770 (76%)	252 (75%)	1080 (68%)	611 (69%)
Race:				
ASIAN	37 (4%)	8 (2%)	1 (<1%)	1 (<1%)
BLACK	85 (8%)	34 (10%)	132 (8%)	107 (12%)
CAUCASIAN	823 (81%)	261 (78%)	248 (16%)	127 (14%)
HISPANIC	60 (6%)	29 (9%)	1203 (76%)	644 (73%)
OTHER	13 (1%)	4 (1%)	4 (<1%)	3 (<1%)
Weight (kg):				
Mean	79.06	80.78	67.32	67.16
Median	76.40	78.75	65.55	65.00
Std. Dev.	19.31	19.68	13.81	14.15
Min	44.5	45.5	36.0	39.3
Max	156.8	156.6	129.1	153.0
N	1018	336	1588	882

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\DEMSUM_REGION.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1- DEMSUM_REGION

Table 53

Summary of Demographic Characteristics, Comparing Across Geographic Regions
US vs Latin America, Ages 19-55

	P13 ACWY (N=1018)	P13 Menact (N=336)	P17 ACWY (N=1588)	P17 Menact (N=882)
Height (cm):				
Mean	167.76	167.12	163.29	162.53
Median	166.60	166.40	162.00	162.00
Std. Dev.	9.58	8.89	9.70	9.80
Min	134.6	142.2	139.0	114.0
Max	204.5	190.5	198.0	198.0
N	1018	336	1588	882
Met Entry Criteria?:				
YES	1002 (98%)	330 (98%)	1585 (100%)	880 (100%)
NO	16 (2%)	6 (2%)	3 (<1%)	2 (<1%)

Table 54

Summary of Reactogenicity, Comparing Across Geographic Regions
US vs Latin America, Ages 19-55

Reaction		Number (%) of Subjects P13 ACWY (N=1018)	P13 Menact (N=336)	P17 ACWY (N=1588)	P17 Menact (N=882)
INJECTION SITE					
Pain	N	1018	336	1588	882
	ANY	391 (38%)	137 (41%)	632 (40%)	392 (44%)
	MILD	313 (31%)	116 (35%)	441 (28%)	268 (30%)
	MODERATE	75 (7%)	21 (6%)	150 (9%)	95 (11%)
	SEVERE	3 (<1%)	0	41 (3%)	29 (3%)
Erythema (mm)	N	1018	336	1588	882
	ANY	167 (16%)	41 (12%)	207 (13%)	105 (12%)
	>0 - 25 mm	121 (12%)	35 (10%)	173 (11%)	88 (10%)
	>25 - 50 mm	18 (2%)	3 (1%)	17 (1%)	10 (1%)
	> 50 mm	28 (3%)	3 (1%)	17 (1%)	7 (1%)
Induration (mm)	N	1018	336	1588	882
	ANY	128 (13%)	29 (9%)	179 (11%)	115 (13%)
	>0 - 25 mm	92 (9%)	25 (7%)	154 (10%)	93 (11%)
	>25 - 50 mm	22 (2%)	3 (1%)	12 (1%)	12 (1%)
	> 50 mm	14 (1%)	1 (<1%)	13 (1%)	10 (1%)
SYSTEMIC					
Chills	N	1018	336	1588	882
	ANY	41 (4%)	12 (4%)	124 (8%)	70 (8%)
	MILD	31 (3%)	8 (2%)	72 (5%)	47 (5%)
	MODERATE	9 (1%)	4 (1%)	33 (2%)	18 (2%)
	SEVERE	1 (<1%)	0	19 (1%)	5 (1%)
Nausea	N	1018	336	1588	882
	ANY	73 (7%)	18 (5%)	112 (7%)	77 (9%)
	MILD	48 (5%)	12 (4%)	85 (5%)	55 (6%)
	MODERATE	21 (2%)	5 (1%)	17 (1%)	18 (2%)
	SEVERE	4 (<1%)	1 (<1%)	10 (1%)	4 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJSUM_REGION.SAS(WARTERO) 10JUL08, 08:37 SAS.9.1 - PINJSUM_REGION

Table 54

Summary of Reactogenicity, Comparing Across Geographic Regions
US vs Latin America, Ages 19-55

Reaction		Number (%) of Subjects P13 ACWY (N=1018)	P13 Menact (N=336)	P17 ACWY (N=1588)	P17 Menact (N=882)
SYSTEMIC					
Malaise	N	1018	336	1588	882
	ANY	102 (10%)	34 (10%)	309 (19%)	186 (21%)
	MILD	60 (6%)	21 (6%)	190 (12%)	120 (14%)
	MODERATE	33 (3%)	8 (2%)	76 (5%)	54 (6%)
	SEVERE	9 (1%)	5 (1%)	43 (3%)	12 (1%)
Myalgia	N	1018	336	1588	882
	ANY	142 (14%)	50 (15%)	197 (12%)	131 (15%)
	MILD	100 (10%)	35 (10%)	114 (7%)	77 (9%)
	MODERATE	37 (4%)	10 (3%)	58 (4%)	44 (5%)
	SEVERE	5 (<1%)	5 (1%)	25 (2%)	10 (1%)
Arthralgia	N	1018	336	1588	882
	ANY	60 (6%)	20 (6%)	118 (7%)	76 (9%)
	MILD	40 (4%)	13 (4%)	75 (5%)	44 (5%)
	MODERATE	16 (2%)	4 (1%)	27 (2%)	25 (3%)
	SEVERE	4 (<1%)	3 (1%)	16 (1%)	7 (1%)
Headache	N	1018	336	1588	882
	ANY	253 (25%)	84 (25%)	421 (27%)	254 (29%)
	MILD	163 (16%)	56 (17%)	271 (17%)	157 (18%)
	MODERATE	74 (7%)	23 (7%)	101 (6%)	71 (8%)
	SEVERE	16 (2%)	5 (1%)	49 (3%)	26 (3%)
Rash	N	1018	336	1588	882
	ANY	25 (2%)	2 (1%)	53 (3%)	22 (2%)
	OTHER	9 (1%)	2 (1%)	12 (1%)	5 (1%)
	URTICARIAL	16 (2%)	0	41 (3%)	17 (2%)
Fever (>= 38C)	N	1016	336	1587	882
	YES	9 (1%)	2 (1%)	56 (4%)	31 (4%)
	NO	1007 (99%)	334 (99%)	1531 (96%)	851 (96%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJSUM_REGION.SAS(WARTERO) 10JUL08, 08:37 SAS.9.1 - PINJSUM_REGION

Table 54

Summary of Reactogenicity, Comparing Across Geographic Regions
US vs Latin America, Ages 19-55

Reaction		Number (%) of Subjects P13 ACWY (N=1018)	P13 Menact (N=336)	P17 ACWY (N=1588)	P17 Menact (N=882)
OTHER					
Stayed Home	N	1006	333	1585	880
	YES	17 (2%)	3 (1%)	75 (5%)	46 (5%)
	NO	989 (98%)	330 (99%)	1510 (95%)	834 (95%)
Analgesic Antipyretics	N	1018	336	1588	881
	YES	240 (24%)	74 (22%)	250 (16%)	148 (17%)
	NO	778 (76%)	262 (78%)	1338 (84%)	733 (83%)
Temperature (C)	N	1016	336	1587	882
	<38 C	1007 (99%)	334 (99%)	1531 (96%)	851 (96%)
	38 - 38.9 C	6 (1%)	1 (<1%)	42 (3%)	22 (2%)
	39.0 - 39.9 C	3 (<1%)	1 (<1%)	10 (1%)	7 (1%)
	>= 40 C	0	0	4 (<1%)	2 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINJSUM_REGION.SAS(WARTERO) 10JUL08, 08:37 SAS.9.1 - PINJSUM_REGION

Table 55

Summary of Treatment-emergent Adverse Events During Month 1 in Descending Frequency, Comparing across Regions
Adverse Events Occurring in at least 1% of Subjects
US vs Latin America, Ages 19-55

MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
HEADACHE	16 (2%)	4 (1%)	44 (3%)	24 (3%)
MALAISE	8 (1%)	0	26 (2%)	7 (1%)
NASOPHARYNGITIS	4 (<1%)	0	26 (2%)	12 (1%)
PHARYNGOLARYNGEAL PAIN	16 (2%)	5 (1%)	3 (<1%)	2 (<1%)
ARTHRALGIA	8 (1%)	0	14 (1%)	13 (1%)
INJECTION SITE ERYTHEMA	13 (1%)	1 (<1%)	8 (1%)	0
DIZZINESS	4 (<1%)	2 (1%)	10 (1%)	11 (1%)
INJECTION SITE PAIN	3 (<1%)	1 (<1%)	19 (1%)	5 (1%)
SINUSITIS	5 (<1%)	4 (1%)	2 (<1%)	1 (<1%)
ABDOMINAL PAIN	1 (<1%)	1 (<1%)	9 (1%)	10 (1%)
PAIN IN EXTREMITY	7 (1%)	1 (<1%)	4 (<1%)	10 (1%)
INJECTION SITE PRURITUS	11 (1%)	1 (<1%)	5 (<1%)	3 (<1%)
MYALGIA	8 (1%)	2 (1%)	17 (1%)	8 (1%)
BACK PAIN	10 (1%)	1 (<1%)	12 (1%)	9 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUMFRQ_REGION_M1

Table 56

Summary of Treatment-emergent Adverse Events During Months 2 to 6 in Descending Frequency, Comparing across Regions
Adverse Events Occurring in at least 1% of Subjects
US vs Latin America, Ages 19-55

MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M26.SAS(WARTERO) 10JUL08, 08:23 SAS.9.1 - AESUMFRQ_REGION_M26

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
ANY ADVERSE EVENT	184 (18%)	60 (18%)	306 (19%)	187 (21%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	4 (<1%)	1 (<1%)	9 (1%)	2 (<1%)
LYMPH NODE PAIN	1 (<1%)	0	0	0
LYMPHADENOPATHY	3 (<1%)	1 (<1%)	9 (1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	1 (<1%)	6 (<1%)	7 (1%)
EAR PAIN	1 (<1%)	0	1 (<1%)	3 (<1%)
MOTION SICKNESS	0	0	0	1 (<1%)
TINNITUS	0	0	2 (<1%)	0
VERTIGO	0	1 (<1%)	3 (<1%)	3 (<1%)
EYE DISORDERS	5 (<1%)	0	3 (<1%)	4 (<1%)
BLEPHARITIS	0	0	1 (<1%)	1 (<1%)
CONJUNCTIVITIS	1 (<1%)	0	1 (<1%)	1 (<1%)
CONJUNCTIVITIS ALLERGIC	0	0	0	1 (<1%)
EYE DISCHARGE	1 (<1%)	0	0	0
EYE IRRITATION	1 (<1%)	0	1 (<1%)	0
EYE PAIN	0	0	0	1 (<1%)
EYE SWELLING	1 (<1%)	0	0	0
TRICHIASIS	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	28 (3%)	11 (3%)	54 (3%)	35 (4%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
GASTROINTESTINAL DISORDERS				
ABDOMINAL DISTENSION	0	0	0	1 (<1%)
ABDOMINAL PAIN	1 (<1%)	1 (<1%)	9 (1%)	10 (1%)
ABDOMINAL PAIN UPPER	4 (<1%)	0	4 (<1%)	1 (<1%)
APHTHOUS STOMATITIS	0	1 (<1%)	0	0
COLITIS	0	0	0	1 (<1%)
CONSTIPATION	1 (<1%)	0	1 (<1%)	1 (<1%)
DIARRHOEA	8 (1%)	3 (1%)	13 (1%)	7 (1%)
DRY MOUTH	1 (<1%)	0	0	1 (<1%)
DYSPEPSIA	3 (<1%)	0	5 (<1%)	3 (<1%)
FOOD POISONING	0	0	2 (<1%)	0
GASTRITIS	0	0	4 (<1%)	2 (<1%)
GASTROINTESTINAL INFLAMMATION	0	0	0	1 (<1%)
GASTROINTESTINAL PAIN	1 (<1%)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (<1%)	0	0	0
GINGIVAL PAIN	0	0	1 (<1%)	0
GLOSSODYNIA	1 (<1%)	0	0	0
HAEMORRHOIDS	1 (<1%)	0	1 (<1%)	0
HYPERCHLORHYDRIA	0	0	2 (<1%)	0
LIP OEDEMA	0	0	0	1 (<1%)
MELAENA	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
GASTROINTESTINAL DISORDERS				
NAUSEA	6 (1%)	1 (<1%)	9 (1%)	4 (<1%)
ODYNOPHAGIA	0	0	2 (<1%)	1 (<1%)
ORAL PAIN	1 (<1%)	0	0	0
STOMACH DISCOMFORT	2 (<1%)	2 (1%)	0	0
STOMATITIS	1 (<1%)	0	0	0
TOOTHACHE	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
VOMITING	1 (<1%)	1 (<1%)	5 (<1%)	4 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	45 (4%)	8 (2%)	78 (5%)	29 (3%)
APPLICATION SITE PRURITUS	0	0	0	1 (<1%)
ASTHENIA	0	0	1 (<1%)	2 (<1%)
AXILLARY PAIN	2 (<1%)	0	1 (<1%)	0
CHEST PAIN	2 (<1%)	0	2 (<1%)	1 (<1%)
CHILLS	1 (<1%)	0	8 (1%)	2 (<1%)
DISCOMFORT	1 (<1%)	0	0	0
FATIGUE	7 (1%)	1 (<1%)	2 (<1%)	0
FEELING HOT	0	0	2 (<1%)	1 (<1%)
INDURATION	1 (<1%)	0	5 (<1%)	1 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	1 (<1%)	9 (1%)	2 (<1%)
INJECTION SITE BRUISING	1 (<1%)	1 (<1%)	0	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
GEN. DISORDERS & ADMIN. SITE COND.				
INJECTION SITE ERYTHEMA	13 (1%)	1 (<1%)	8 (1%)	0
INJECTION SITE HAEMORRHAGE	0	0	3 (<1%)	1 (<1%)
INJECTION SITE INDURATION	8 (1%)	0	4 (<1%)	1 (<1%)
INJECTION SITE IRRITATION	0	0	1 (<1%)	0
INJECTION SITE MASS	1 (<1%)	0	0	0
INJECTION SITE OEDEMA	0	0	2 (<1%)	0
INJECTION SITE PAIN	3 (<1%)	1 (<1%)	19 (1%)	5 (1%)
INJECTION SITE PRURITUS	11 (1%)	1 (<1%)	5 (<1%)	3 (<1%)
INJECTION SITE REACTION	1 (<1%)	0	1 (<1%)	0
INJECTION SITE SWELLING	1 (<1%)	0	0	0
INJECTION SITE WARMTH	5 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
MALAISE	8 (1%)	0	26 (2%)	7 (1%)
OEDEMA PERIPHERAL	1 (<1%)	0	1 (<1%)	0
PAIN	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
PYREXIA	1 (<1%)	0	2 (<1%)	0
TENDERNESS	1 (<1%)	0	0	0
THIRST	1 (<1%)	0	1 (<1%)	0
HEPATO-BILIARY DISORDERS	0	0	1 (<1%)	0
BILIARY COLIC	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
IMMUNE SYSTEM DISORDERS	2 (<1%)	1 (<1%)	0	0
DRUG HYPERSENSITIVITY	0	1 (<1%)	0	0
HYPERSENSITIVITY	1 (<1%)	0	0	0
MULTIPLE ALLERGIES	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	41 (4%)	15 (4%)	99 (6%)	59 (7%)
ABSCESS LIMB	0	0	1 (<1%)	0
ABSCESS ORAL	0	0	1 (<1%)	0
ACUTE SINUSITIS	0	0	1 (<1%)	1 (<1%)
ACUTE TONSILLITIS	0	0	1 (<1%)	0
BACTERIAL INFECTION	1 (<1%)	0	0	0
BREAST CELLULITIS	0	0	0	1 (<1%)
BRONCHITIS	2 (<1%)	2 (1%)	2 (<1%)	2 (<1%)
BRONCHOPNEUMONIA	0	0	1 (<1%)	0
CELLULITIS	1 (<1%)	0	0	0
CONJUNCTIVITIS BACTERIAL	0	0	0	1 (<1%)
CYSTITIS	1 (<1%)	0	0	2 (<1%)
EAR INFECTION	2 (<1%)	0	2 (<1%)	0
FUNGAL INFECTION	1 (<1%)	3 (1%)	0	0
FUNGAL SKIN INFECTION	0	0	0	2 (<1%)
GASTROENTERITIS	0	0	7 (<1%)	5 (1%)
GASTROENTERITIS VIRAL	2 (<1%)	0	0	1 (<1%)
HELICOBACTER INFECTION	1 (<1%)	0	0	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
INFECTIONS & INFESTATIONS				
HERPES ZOSTER	0	0	0	1 (<1%)
HORDEOLUM	0	0	1 (<1%)	0
INFECTION PARASITIC	0	0	0	1 (<1%)
INFLUENZA	0	0	3 (<1%)	2 (<1%)
INJECTION SITE INFECTION	0	0	1 (<1%)	0
LARYNGITIS	0	0	0	1 (<1%)
MASTITIS	0	0	1 (<1%)	0
NAIL BED INFECTION	0	1 (<1%)	0	0
NASOPHARYNGITIS	4 (<1%)	0	26 (2%)	12 (1%)
OMPHALITIS	0	0	1 (<1%)	0
ONYCHOMYCOSIS	0	0	0	1 (<1%)
ORAL HERPES	1 (<1%)	1 (<1%)	3 (<1%)	4 (<1%)
OTITIS EXTERNA	0	0	0	1 (<1%)
OTITIS MEDIA	1 (<1%)	1 (<1%)	0	1 (<1%)
PELVIC INFLAMMATORY DISEASE	0	0	2 (<1%)	0
PERTUSSIS	1 (<1%)	0	0	0
PHARYNGITIS	1 (<1%)	0	9 (1%)	5 (1%)
PHARYNGITIS BACTERIAL	0	0	0	1 (<1%)
PHARYNGITIS STREPTOCOCCAL	2 (<1%)	2 (1%)	0	0
POSTOPERATIVE WOUND INFECTION	0	0	0	1 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
INFECTIONS & INFESTATIONS				
RESPIRATORY TRACT INFECTION	0	0	1 (<1%)	0
RHINITIS	0	0	11 (1%)	5 (1%)
SINUSITIS	5 (<1%)	4 (1%)	2 (<1%)	1 (<1%)
SYPHILIS	0	0	0	1 (<1%)
TINEA CRURIS	0	0	0	1 (<1%)
TONSILLITIS	0	0	2 (<1%)	0
TOOTH ABSCESS	2 (<1%)	1 (<1%)	0	0
TOOTH INFECTION	0	1 (<1%)	3 (<1%)	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	3 (<1%)	0	4 (<1%)	5 (1%)
URINARY TRACT INFECTION	7 (1%)	1 (<1%)	1 (<1%)	5 (1%)
VAGINAL INFECTION	2 (<1%)	0	0	0
VAGINITIS BACTERIAL	0	1 (<1%)	0	0
VIRAL INFECTION	1 (<1%)	0	8 (1%)	1 (<1%)
VIRAL PHARYNGITIS	0	0	3 (<1%)	1 (<1%)
VULVOVAGINAL MYCOTIC INFECTION	1 (<1%)	0	1 (<1%)	0
WOUND INFECTION	0	0	1 (<1%)	0
INJURY & POISONING	6 (1%)	3 (1%)	6 (<1%)	4 (<1%)
ACCIDENTAL NEEDLE STICK	0	0	1 (<1%)	0
ANIMAL BITE	1 (<1%)	0	0	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
INJURY & POISONING				
CONTUSION	1 (<1%)	0	0	0
FALL	0	1 (<1%)	0	0
HEAD INJURY	0	0	1 (<1%)	0
HEAT EXHAUSTION	1 (<1%)	0	0	0
INJURY	0	0	2 (<1%)	2 (<1%)
JOINT SPRAIN	2 (<1%)	0	0	1 (<1%)
MULTIPLE INJURIES	0	0	0	1 (<1%)
MUSCLE STRAIN	0	0	1 (<1%)	0
PROCEDURAL PAIN	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	0	0
SKIN LACERATION	0	1 (<1%)	0	0
SUNBURN	0	1 (<1%)	0	0
WOUND	1 (<1%)	0	1 (<1%)	0
INVESTIGATIONS	1 (<1%)	1 (<1%)	0	0
BLOOD POTASSIUM DECREASED	0	1 (<1%)	0	0
BLOOD PRESSURE INCREASED	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	0	0	0	2 (<1%)
INCREASED APPETITE	0	0	0	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
MUSCULO., CONNECT. TIS. & BONE DIS.	36 (4%)	9 (3%)	46 (3%)	42 (5%)
ARTHRALGIA	8 (1%)	0	14 (1%)	13 (1%)
BACK PAIN	10 (1%)	1 (<1%)	12 (1%)	9 (1%)
COSTOCHONDRITIS	0	0	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)	0	0
JOINT HYPEREXTENSION	1 (<1%)	0	0	0
JOINT STIFFNESS	1 (<1%)	0	0	0
MEDIAL TIBIAL STRESS SYNDROME	1 (<1%)	0	0	0
MUSCLE CONTRACTURE	0	0	1 (<1%)	0
MUSCLE SPASMS	4 (<1%)	0	0	5 (1%)
MUSCULAR WEAKNESS	0	0	1 (<1%)	0
MUSCULOSKELETAL CHEST PAIN	0	1 (<1%)	0	0
MUSCULOSKELETAL PAIN	2 (<1%)	1 (<1%)	0	1 (<1%)
MUSCULOSKELETAL STIFFNESS	1 (<1%)	2 (1%)	0	0
MYALGIA	8 (1%)	2 (1%)	17 (1%)	8 (1%)
NECK PAIN	4 (<1%)	0	3 (<1%)	1 (<1%)
OSTEOCHONDROSIS	0	0	1 (<1%)	0
PAIN IN EXTREMITY	7 (1%)	1 (<1%)	4 (<1%)	10 (1%)
SPINAL DEFORMITY	0	0	1 (<1%)	0
TENDONITIS	0	0	1 (<1%)	0
TORTICOLLIS	0	0	0	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)				
POLYCYTHAEMIA VERA	0	0	1 (<1%)	0
UTERINE LEIOMYOMA	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	30 (3%)	9 (3%)	68 (4%)	43 (5%)
BURNING SENSATION	0	0	1 (<1%)	1 (<1%)
CARPAL TUNNEL SYNDROME	0	0	0	2 (<1%)
DIZZINESS	4 (<1%)	2 (1%)	10 (1%)	11 (1%)
HEADACHE	16 (2%)	4 (1%)	44 (3%)	24 (3%)
MIGRAINE	4 (<1%)	0	5 (<1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	0	0	1 (<1%)	0
NEURALGIA	0	1 (<1%)	0	0
PARAESTHESIA	0	0	6 (<1%)	4 (<1%)
SCIATICA	0	1 (<1%)	1 (<1%)	1 (<1%)
SINUS HEADACHE	7 (1%)	1 (<1%)	0	0
SOMNOLENCE	0	0	5 (<1%)	2 (<1%)
SYNCOPE	0	0	1 (<1%)	0
SYNCOPE VASOVAGAL	1 (<1%)	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	8 (1%)	1 (<1%)	4 (<1%)	4 (<1%)
ANXIETY	1 (<1%)	0	1 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
PSYCHIATRIC DISORDERS				
DEPRESSION	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
INSOMNIA	4 (<1%)	0	1 (<1%)	1 (<1%)
POST-TRAUMATIC STRESS DISORDER	1 (<1%)	0	0	0
RESTLESSNESS	1 (<1%)	0	0	0
RENAL & URINARY DISORDERS	3 (<1%)	0	0	0
CALCULUS URETERIC	1 (<1%)	0	0	0
NEPHROLITHIASIS	2 (<1%)	0	0	0
REPRODUCT. SYS. & BREAST DISORDERS	6 (1%)	4 (1%)	14 (1%)	7 (1%)
BREAST PAIN	0	0	0	1 (<1%)
DYSMENORRHOEA	5 (<1%)	2 (1%)	14 (1%)	3 (<1%)
OLIGOMENORRHOEA	1 (<1%)	0	0	0
POSTMENOPAUSAL HAEMORRHAGE	0	1 (<1%)	0	0
PREMENSTRUAL SYNDROME	0	1 (<1%)	0	0
VAGINAL DISCHARGE	0	0	0	2 (<1%)
VULVOVAGINAL BURNING SENSATION	0	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	27 (3%)	7 (2%)	17 (1%)	8 (1%)
BRONCHIAL HYPERREACTIVITY	0	0	1 (<1%)	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
RESP., THORACIC & MEDIASTINAL DIS.				
COUGH	4 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
DRY THROAT	1 (<1%)	0	0	0
DYSPHONIA	0	0	1 (<1%)	0
DYSPNOEA	2 (<1%)	0	0	1 (<1%)
EPISTAXIS	0	0	3 (<1%)	1 (<1%)
NASAL CONGESTION	6 (1%)	0	0	1 (<1%)
NASAL DRYNESS	1 (<1%)	0	0	0
PHARYNGOLARYNGEAL PAIN	16 (2%)	5 (1%)	3 (<1%)	2 (<1%)
PULMONARY CONGESTION	0	2 (1%)	0	0
RHINITIS ALLERGIC	0	0	5 (<1%)	2 (<1%)
RHINORRHOEA	3 (<1%)	0	0	1 (<1%)
SINUS CONGESTION	2 (<1%)	1 (<1%)	0	0
THROAT IRRITATION	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	7 (1%)	4 (1%)	21 (1%)	15 (2%)
ACNE	0	0	0	1 (<1%)
ANGIOEDEMA	0	0	0	1 (<1%)
DERMAL CYST	1 (<1%)	0	0	0
DERMATITIS ALLERGIC	0	0	1 (<1%)	0
DERMATITIS ATOPIC	0	0	0	1 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 57

Summary of Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
SKIN & SUBCUTANEOUS TIS. DISORDERS				
DERMATITIS CONTACT	1 (<1%)	1 (<1%)	0	0
ECCHYMOSIS	0	0	1 (<1%)	1 (<1%)
ERYTHEMA	3 (<1%)	0	7 (<1%)	3 (<1%)
HYPERHIDROSIS	0	0	2 (<1%)	3 (<1%)
INGROWING NAIL	0	0	0	1 (<1%)
PRURIGO	0	0	0	1 (<1%)
PRURITUS	0	0	3 (<1%)	0
PRURITUS GENERALISED	0	0	1 (<1%)	0
RASH	2 (<1%)	2 (1%)	8 (1%)	2 (<1%)
RASH MACULAR	0	0	0	1 (<1%)
SKIN DISCOLOURATION	1 (<1%)	0	0	0
URTICARIA	1 (<1%)	1 (<1%)	1 (<1%)	0
VASCULAR DISORDERS	3 (<1%)	2 (1%)	4 (<1%)	4 (<1%)
FLUSHING	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
HYPERTENSION	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)
HYPERTENSIVE CRISIS	0	0	0	1 (<1%)
HYPOTENSION	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - AESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
ANY ADVERSE EVENT	71 (7%)	17 (5%)	145 (9%)	78 (9%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	2 (<1%)	1 (<1%)	8 (1%)	1 (<1%)
LYMPHADENOPATHY	2 (<1%)	1 (<1%)	8 (1%)	1 (<1%)
EAR & LABYRINTH DISORDERS	0	1 (<1%)	6 (<1%)	4 (<1%)
EAR PAIN	0	0	1 (<1%)	1 (<1%)
MOTION SICKNESS	0	0	0	1 (<1%)
TINNITUS	0	0	2 (<1%)	0
VERTIGO	0	1 (<1%)	3 (<1%)	2 (<1%)
EYE DISORDERS	1 (<1%)	0	0	0
EYE SWELLING	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	10 (1%)	1 (<1%)	17 (1%)	14 (2%)
ABDOMINAL DISTENSION	0	0	0	1 (<1%)
ABDOMINAL PAIN	0	1 (<1%)	2 (<1%)	3 (<1%)
ABDOMINAL PAIN UPPER	2 (<1%)	0	1 (<1%)	0
DIARRHOEA	3 (<1%)	0	6 (<1%)	3 (<1%)
DRY MOUTH	0	0	0	1 (<1%)
DYSPEPSIA	0	0	1 (<1%)	0
GASTRITIS	0	0	0	1 (<1%)
NAUSEA	5 (<1%)	0	6 (<1%)	2 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
GASTROINTESTINAL DISORDERS				
ORAL PAIN	1 (<1%)	0	0	0
STOMACH DISCOMFORT	2 (<1%)	0	0	0
VOMITING	0	0	2 (<1%)	3 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	37 (4%)	6 (2%)	59 (4%)	20 (2%)
ASTHENIA	0	0	0	2 (<1%)
AXILLARY PAIN	2 (<1%)	0	1 (<1%)	0
CHEST PAIN	0	0	2 (<1%)	0
CHILLS	0	0	5 (<1%)	1 (<1%)
FATIGUE	6 (1%)	1 (<1%)	2 (<1%)	0
FEELING HOT	0	0	2 (<1%)	1 (<1%)
INDURATION	1 (<1%)	0	5 (<1%)	1 (<1%)
INFLUENZA LIKE ILLNESS	1 (<1%)	0	1 (<1%)	0
INJECTION SITE BRUISING	1 (<1%)	1 (<1%)	0	0
INJECTION SITE ERYTHEMA	13 (1%)	1 (<1%)	8 (1%)	0
INJECTION SITE HAEMORRHAGE	0	0	2 (<1%)	1 (<1%)
INJECTION SITE INDURATION	8 (1%)	0	4 (<1%)	1 (<1%)
INJECTION SITE IRRITATION	0	0	1 (<1%)	0
INJECTION SITE MASS	1 (<1%)	0	0	0
INJECTION SITE OEDEMA	0	0	2 (<1%)	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
GEN. DISORDERS & ADMIN. SITE COND.				
INJECTION SITE PAIN	3 (<1%)	1 (<1%)	19 (1%)	5 (1%)
INJECTION SITE PRURITUS	11 (1%)	1 (<1%)	4 (<1%)	3 (<1%)
INJECTION SITE REACTION	0	0	1 (<1%)	0
INJECTION SITE SWELLING	1 (<1%)	0	0	0
INJECTION SITE WARMTH	5 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
MALAISE	6 (1%)	0	16 (1%)	3 (<1%)
OEDEMA PERIPHERAL	1 (<1%)	0	0	0
PAIN	0	0	2 (<1%)	0
PYREXIA	0	0	2 (<1%)	0
THIRST	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	4 (<1%)	1 (<1%)	23 (1%)	11 (1%)
CELLULITIS	1 (<1%)	0	0	0
CONJUNCTIVITIS BACTERIAL	0	0	0	1 (<1%)
GASTROENTERITIS	0	0	3 (<1%)	0
GASTROENTERITIS VIRAL	1 (<1%)	0	0	0
INFLUENZA	0	0	0	1 (<1%)
INJECTION SITE INFECTION	0	0	1 (<1%)	0
NASOPHARYNGITIS	1 (<1%)	0	9 (1%)	4 (<1%)
ORAL HERPES	0	0	2 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
INFECTIONS & INFESTATIONS				
OTITIS MEDIA	0	0	0	1 (<1%)
PHARYNGITIS	0	0	2 (<1%)	0
RESPIRATORY TRACT INFECTION	0	0	1 (<1%)	0
RHINITIS	0	0	1 (<1%)	0
SINUSITIS	0	1 (<1%)	0	0
UPPER RESPIRATORY TRACT INFECTION	1 (<1%)	0	1 (<1%)	2 (<1%)
VIRAL INFECTION	0	0	4 (<1%)	1 (<1%)
INJURY & POISONING	1 (<1%)	0	0	0
HEAT EXHAUSTION	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	0	0	0	2 (<1%)
INCREASED APPETITE	0	0	0	2 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	11 (1%)	1 (<1%)	21 (1%)	15 (2%)
ARTHRALGIA	4 (<1%)	0	8 (1%)	9 (1%)
BACK PAIN	3 (<1%)	0	5 (<1%)	1 (<1%)
MUSCLE SPASMS	0	0	0	1 (<1%)
MUSCULAR WEAKNESS	0	0	1 (<1%)	0
MUSCULOSKELETAL PAIN	1 (<1%)	1 (<1%)	0	0

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
...Continued from previous page				
MUSCULO., CONNECT. TIS. & BONE DIS.				
MUSCULOSKELETAL STIFFNESS	1 (<1%)	0	0	0
MYALGIA	5 (<1%)	0	11 (1%)	5 (1%)
NECK PAIN	4 (<1%)	0	0	0
PAIN IN EXTREMITY	1 (<1%)	0	0	2 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	0	1 (<1%)	0
POLYCYTHAEMIA VERA	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	13 (1%)	3 (1%)	50 (3%)	27 (3%)
BURNING SENSATION	0	0	1 (<1%)	1 (<1%)
DIZZINESS	2 (<1%)	1 (<1%)	8 (1%)	9 (1%)
HEADACHE	7 (1%)	1 (<1%)	31 (2%)	16 (2%)
MIGRAINE	1 (<1%)	0	3 (<1%)	0
MUSCLE CONTRACTIONS INVOLUNTARY	0	0	1 (<1%)	0
PARAESTHESIA	0	0	5 (<1%)	1 (<1%)
SINUS HEADACHE	2 (<1%)	1 (<1%)	0	0
SOMNOLENCE	0	0	4 (<1%)	2 (<1%)
SYNCOPE	0	0	1 (<1%)	0
SYNCOPE VASOVAGAL	1 (<1%)	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
PSYCHIATRIC DISORDERS	4 (<1%)	0	0	1 (<1%)
DEPRESSION	1 (<1%)	0	0	1 (<1%)
INSOMNIA	3 (<1%)	0	0	0
RESTLESSNESS	1 (<1%)	0	0	0
REPRODUCT. SYS. & BREAST DISORDERS	0	0	1 (<1%)	0
DYSMENORRHOEA	0	0	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	5 (<1%)	2 (1%)	2 (<1%)	3 (<1%)
COUGH	0	1 (<1%)	0	1 (<1%)
EPISTAXIS	0	0	0	1 (<1%)
PHARYNGOLARYNGEAL PAIN	5 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
RHINITIS ALLERGIC	0	0	1 (<1%)	0
RHINORRHOEA	0	0	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	5 (<1%)	1 (<1%)	17 (1%)	9 (1%)
DERMATITIS ALLERGIC	0	0	1 (<1%)	0
ECCHYMOSIS	0	0	1 (<1%)	1 (<1%)
ERYTHEMA	3 (<1%)	0	6 (<1%)	3 (<1%)
HYPERHIDROSIS	0	0	2 (<1%)	2 (<1%)
PRURITUS	0	0	1 (<1%)	0
RASH	2 (<1%)	1 (<1%)	8 (1%)	2 (<1%)
RASH MACULAR	0	0	0	1 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 58

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
...Continued from previous page				
SKIN & SUBCUTANEOUS TIS. DISORDERS				
SKIN DISCOLOURATION	1 (<1%)	0	0	0
URTICARIA	1 (<1%)	0	1 (<1%)	0
VASCULAR DISORDERS	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
FLUSHING	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M1.SAS(WARTERO) 10JUL08, 08:22 SAS.9.1 - PRAESUM_REGION_M1

Table 59

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
ANY ADVERSE EVENT	19 (2%)	4 (1%)	11 (1%)	7 (1%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	1 (<1%)	0	0	0
LYMPH NODE PAIN	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	2 (<1%)	0	1 (<1%)	1 (<1%)
NAUSEA	2 (<1%)	0	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	4 (<1%)	0	4 (<1%)	1 (<1%)
AXILLARY PAIN	0	0	1 (<1%)	0
INDURATION	0	0	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0	1 (<1%)	0
MALAISE	2 (<1%)	0	3 (<1%)	1 (<1%)
OEDEMA PERIPHERAL	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	4 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
GASTROENTERITIS	0	0	1 (<1%)	0
HERPES ZOSTER	0	0	0	1 (<1%)
NASOPHARYNGITIS	1 (<1%)	0	0	0
OTITIS MEDIA	1 (<1%)	0	0	0
PHARYNGITIS STREPTOCOCCAL	1 (<1%)	0	0	0
SINUSITIS	1 (<1%)	0	0	0
TOOTH INFECTION	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_REGION_M1.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_REGION_M1

Table 59

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
INJURY & POISONING	1 (<1%)	1 (<1%)	0	0
CONTUSION	1 (<1%)	0	0	0
FALL	0	1 (<1%)	0	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	0	0
WOUND	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	4 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
ARTHRALGIA	2 (<1%)	0	1 (<1%)	2 (<1%)
BACK PAIN	1 (<1%)	0	0	0
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)	0	0
MUSCLE SPASMS	1 (<1%)	0	0	0
MYALGIA	1 (<1%)	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	7 (1%)	1 (<1%)	7 (<1%)	4 (<1%)
HEADACHE	3 (<1%)	0	6 (<1%)	4 (<1%)
MIGRAINE	2 (<1%)	0	1 (<1%)	0
SCIATICA	0	1 (<1%)	0	0
SINUS HEADACHE	1 (<1%)	0	0	0
SYNCOPE VASOVAGAL	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	0	0
DEPRESSION	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_REGION_M1.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_REGION_M1

Table 59

Summary of Severe Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0	1 (<1%)	1 (<1%)
ANGIOEDEMA	0	0	0	1 (<1%)
ERYTHEMA	1 (<1%)	0	0	0
RASH	0	0	1 (<1%)	0
URTICARIA	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_REGION_M1.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - AESUM_SEV_REGION_M1

Table 60

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
ANY ADVERSE EVENT	8 (1%)	0	6 (<1%)	4 (<1%)
GASTROINTESTINAL DISORDERS	2 (<1%)	0	1 (<1%)	0
NAUSEA	2 (<1%)	0	1 (<1%)	0
GEN. DISORDERS & ADMIN. SITE COND.	4 (<1%)	0	4 (<1%)	0
AXILLARY PAIN	0	0	1 (<1%)	0
INDURATION	0	0	1 (<1%)	0
INJECTION SITE PAIN	1 (<1%)	0	1 (<1%)	0
MALAISE	2 (<1%)	0	3 (<1%)	0
OEDEMA PERIPHERAL	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	1 (<1%)	1 (<1%)
ARTHRALGIA	1 (<1%)	0	1 (<1%)	1 (<1%)
MYALGIA	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	3 (<1%)	0	3 (<1%)	3 (<1%)
HEADACHE	2 (<1%)	0	3 (<1%)	3 (<1%)
SYNCOPE VASOVAGAL	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	0	0
DEPRESSION	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_REGION_M1.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - PRAESUM_SEV_REGION_M1

Table 60

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Month 1, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0	1 (<1%)	0
ERYTHEMA	1 (<1%)	0	0	0
RASH	0	0	1 (<1%)	0
URTICARIA	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESUM_SEV_REGION_M1.SAS(WARTERO) 10JUL08, 08:16 SAS.9.1 - PRAESUM_SEV_REGION_M1

Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)
ANY ADVERSE EVENT	86 (9%)	13 (4%)	105 (7%)	74 (8%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	0	0	2 (<1%)	2 (<1%)
ANAEMIA	0	0	2 (<1%)	1 (<1%)
DEFICIENCY ANAEMIA	0	0	0	1 (<1%)
CARDIAC DISORDERS	1 (<1%)	0	0	4 (<1%)
EXTRASYSTOLES	0	0	0	1 (<1%)
PALPITATIONS	1 (<1%)	0	0	1 (<1%)
TACHYCARDIA	0	0	0	3 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0
HYPOACUSIS	1 (<1%)	0	0	0
VERTIGO	0	0	1 (<1%)	0
ENDOCRINE DISORDERS	1 (<1%)	0	1 (<1%)	3 (<1%)
HYPOTHYROIDISM	1 (<1%)	0	1 (<1%)	3 (<1%)
EYE DISORDERS	0	0	2 (<1%)	1 (<1%)
BLEPHARITIS	0	0	1 (<1%)	0
PTERYGIUM	0	0	0	1 (<1%)
RETINAL DETACHMENT	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M26.SAS(WARTERO) 10JUL08, 08:23 SAS.9.1 - AESUM_REGION_M26

Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
GASTROINTESTINAL DISORDERS	7 (1%)	1 (<1%)	19 (1%)	8 (1%)
ABDOMINAL DISCOMFORT	1 (<1%)	0	0	0
ABDOMINAL DISTENSION	0	0	1 (<1%)	0
ABDOMINAL HERNIA	0	0	1 (<1%)	0
ABDOMINAL PAIN	0	1 (<1%)	2 (<1%)	3 (<1%)
DIARRHOEA	1 (<1%)	0	0	0
DIVERTICULUM INTESTINAL	1 (<1%)	0	0	0
GASTRIC ULCER	0	0	1 (<1%)	0
GASTRITIS	0	0	10 (1%)	3 (<1%)
GASTROOESOPHAGEAL REFLUX DISEASE	3 (<1%)	0	0	0
IRRITABLE BOWEL SYNDROME	1 (<1%)	0	3 (<1%)	1 (<1%)
MALLORY-WEISS SYNDROME	0	0	1 (<1%)	0
NAUSEA	1 (<1%)	0	0	0
TOOTHACHE	0	0	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	5 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
CHEST PAIN	2 (<1%)	1 (<1%)	0	0
FATIGUE	2 (<1%)	0	0	0
GENERALISED OEDEMA	0	0	0	1 (<1%)
HERNIA	0	0	1 (<1%)	0
INFLUENZA LIKE ILLNESS	0	0	1 (<1%)	0
MALAISE	1 (<1%)	0	1 (<1%)	0
PYREXIA	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_REGION_M26.SAS(WARTERO) 10JUL08, 08:23 SAS.9.1 - AESUM_REGION_M26

Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)
HEPATO-BILIARY DISORDERS	1 (<1%)	0	0	0
GALLBLADDER POLYP	1 (<1%)	0	0	0
HEPATOMEGALY	1 (<1%)	0	0	0
IMMUNE SYSTEM DISORDERS	1 (<1%)	1 (<1%)	1 (<1%)	0
DRUG HYPERSENSITIVITY	1 (<1%)	1 (<1%)	0	0
HYPERSENSITIVITY	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	20 (2%)	3 (1%)	26 (2%)	12 (1%)
ABSCESS LIMB	1 (<1%)	0	0	0
APPENDICITIS	0	0	1 (<1%)	0
BRONCHITIS	3 (<1%)	1 (<1%)	6 (<1%)	0
CELLULITIS	4 (<1%)	0	1 (<1%)	2 (<1%)
CONJUNCTIVITIS BACTERIAL	0	0	1 (<1%)	0
CYSTITIS	0	0	1 (<1%)	0
EYE INFECTION TOXOPLASMAL	0	0	0	1 (<1%)
FUNGAL INFECTION	1 (<1%)	0	0	0
GASTROENTERITIS VIRAL	0	0	1 (<1%)	0
GENITAL HERPES	0	1 (<1%)	0	0
HELICOBACTER GASTRITIS	2 (<1%)	0	0	0
HERPES ZOSTER	1 (<1%)	0	1 (<1%)	1 (<1%)
HIV INFECTION	0	0	0	1 (<1%)
KIDNEY INFECTION	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
INFECTIONS & INFESTATIONS				
MENINGITIS VIRAL	1 (<1%)	0	0	0
PARASITIC GASTROENTERITIS	0	0	1 (<1%)	0
PERIORBITAL CELLULITIS	1 (<1%)	0	0	0
PHARYNGITIS	0	0	2 (<1%)	0
PILONIDAL CYST	0	1 (<1%)	0	0
PNEUMONIA	6 (1%)	0	3 (<1%)	0
RHINITIS	0	0	1 (<1%)	0
SINUSITIS	1 (<1%)	0	0	0
SUBCUTANEOUS ABSCESS	0	0	3 (<1%)	2 (<1%)
TONSILLITIS	0	0	0	1 (<1%)
TOOTH ABSCESS	0	0	1 (<1%)	0
URINARY TRACT INFECTION	1 (<1%)	0	1 (<1%)	1 (<1%)
VAGINAL INFECTION	0	0	0	1 (<1%)
VAGINITIS BACTERIAL	0	0	1 (<1%)	0
VARICELLA	0	0	1 (<1%)	1 (<1%)
VULVOVAGINITIS TRICHOMONAL	0	0	1 (<1%)	1 (<1%)
INJURY & POISONING	10 (1%)	3 (1%)	17 (1%)	12 (1%)
ANIMAL BITE	0	0	1 (<1%)	0
ANKLE FRACTURE	0	0	0	1 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
INJURY & POISONING				
ARTHROPOD STING	0	0	1 (<1%)	0
BACK INJURY	0	1 (<1%)	0	0
BURNS SECOND DEGREE	0	1 (<1%)	0	0
CLAVICLE FRACTURE	1 (<1%)	0	0	0
CONTUSION	1 (<1%)	0	0	0
EXCORIATION	0	1 (<1%)	0	0
FALL	1 (<1%)	0	0	1 (<1%)
FOOT FRACTURE	0	0	1 (<1%)	0
FRACTURED COCCYX	0	0	1 (<1%)	0
GUN SHOT WOUND	0	0	0	1 (<1%)
HEAD INJURY	0	0	1 (<1%)	1 (<1%)
INJURY	0	0	8 (1%)	2 (<1%)
JOINT DISLOCATION	0	0	1 (<1%)	1 (<1%)
JOINT INJURY	0	0	1 (<1%)	0
JOINT SPRAIN	2 (<1%)	0	1 (<1%)	2 (<1%)
LACERATION	0	0	1 (<1%)	0
MENISCUS LESION	0	0	0	1 (<1%)
OVERDOSE	1 (<1%)	0	0	0
PROCEDURAL PAIN	1 (<1%)	0	0	0
RADIUS FRACTURE	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
INJURY & POISONING				
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	0	0
SKIN LACERATION	1 (<1%)	0	0	0
SOFT TISSUE INJURY	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	1 (<1%)
WOUND	0	0	0	1 (<1%)
INVESTIGATIONS	4 (<1%)	0	0	0
ENDOSCOPY	1 (<1%)	0	0	0
LIVER FUNCTION TEST ABNORMAL	1 (<1%)	0	0	0
TRANSAMINASES INCREASED	1 (<1%)	0	0	0
WEIGHT DECREASED	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	6 (<1%)	1 (<1%)
DYSLIPIDAEMIA	0	0	4 (<1%)	0
HYPERCHOLESTEROLAEMIA	0	0	2 (<1%)	1 (<1%)
HYPERLIPIDAEMIA	2 (<1%)	0	0	0
TYPE 2 DIABETES MELLITUS	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	12 (1%)	1 (<1%)	10 (1%)	10 (1%)
ARTHRALGIA	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
MUSCULO., CONNECT. TIS. & BONE DIS.				
BACK PAIN	2 (<1%)	0	2 (<1%)	5 (1%)
COSTOCHONDRITIS	1 (<1%)	0	0	0
EXOSTOSIS	1 (<1%)	0	0	0
INTERVERTEBRAL DISC PROTRUSION	0	0	2 (<1%)	2 (<1%)
JOINT SWELLING	1 (<1%)	0	0	0
MUSCLE SPASMS	1 (<1%)	1 (<1%)	1 (<1%)	0
MUSCULOSKELETAL PAIN	3 (<1%)	0	0	0
MYALGIA	0	0	1 (<1%)	0
OSTEOARTHRITIS	0	0	1 (<1%)	2 (<1%)
PAIN IN EXTREMITY	1 (<1%)	0	0	1 (<1%)
PLANTAR FASCIITIS	1 (<1%)	0	0	0
SYNOVIAL CYST	0	0	1 (<1%)	0
TEMPOROMANDIBULAR JOINT SYNDROME	1 (<1%)	0	0	0
TENDONITIS	0	0	1 (<1%)	0
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	2 (<1%)	0	3 (<1%)	2 (<1%)
ACROCHORDON	1 (<1%)	0	0	0
BREAST NEOPLASM	0	0	0	1 (<1%)
MELANOCYTIC NAEVUS	1 (<1%)	0	0	0
MORTON'S NEUROMA	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)				
PAPILLOMA	0	0	1 (<1%)	0
UTERINE LEIOMYOMA	0	0	2 (<1%)	1 (<1%)
NERVOUS SYSTEM DISORDERS	8 (1%)	3 (1%)	7 (<1%)	9 (1%)
CARPAL TUNNEL SYNDROME	1 (<1%)	0	0	0
DIZZINESS	1 (<1%)	1 (<1%)	0	1 (<1%)
DYSTONIA	1 (<1%)	0	0	0
EPILEPSY	1 (<1%)	0	0	0
FACIAL PALSY	0	0	0	1 (<1%)
GRAND MAL CONVULSION	1 (<1%)	0	0	0
HEADACHE	0	0	2 (<1%)	4 (<1%)
MIGRAINE	2 (<1%)	0	1 (<1%)	3 (<1%)
PARAESTHESIA	1 (<1%)	0	0	0
PETIT MAL EPILEPSY	1 (<1%)	0	0	0
POST HERPETIC NEURALGIA	0	0	0	1 (<1%)
SOMNOLENCE	0	0	0	1 (<1%)
SYNCOPE	0	0	2 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)	0	0
TENSION HEADACHE	0	0	2 (<1%)	0
TREMOR	0	1 (<1%)	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
PREG., PUERPERIUM & PERINATAL COND.	0	0	4 (<1%)	0
ABORTION SPONTANEOUS	0	0	3 (<1%)	0
ABORTION THREATENED	0	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	9 (1%)	2 (1%)	0	0
ANXIETY	5 (<1%)	0	0	0
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	0	2 (1%)	0	0
CONVERSION DISORDER	1 (<1%)	0	0	0
DEPRESSION	2 (<1%)	0	0	0
MENOPAUSAL DEPRESSION	1 (<1%)	0	0	0
SUICIDE ATTEMPT	1 (<1%)	0	0	0
RENAL & URINARY DISORDERS	1 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
HAEMATURIA	0	0	1 (<1%)	0
NEPHROLITHIASIS	1 (<1%)	2 (1%)	0	0
RENAL COLIC	0	0	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	4 (<1%)	1 (<1%)	4 (<1%)	2 (<1%)
BREAST MASS	0	0	1 (<1%)	0
BREAST PAIN	1 (<1%)	0	0	1 (<1%)
ERECTILE DYSFUNCTION	0	1 (<1%)	0	0
MENOPAUSAL SYMPTOMS	1 (<1%)	0	0	0
OVARIAN CYST	1 (<1%)	0	2 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
REPRODUCT. SYS. & BREAST DISORDERS				
VAGINAL DISCHARGE	0	0	1 (<1%)	1 (<1%)
VAGINAL HAEMORRHAGE	1 (<1%)	0	0	0
RESP., THORACIC & MEDIASTINAL DIS.	10 (1%)	0	4 (<1%)	4 (<1%)
ASTHMA	4 (<1%)	0	0	0
ASTHMATIC CRISIS	0	0	2 (<1%)	0
BRONCHIAL HYPERREACTIVITY	1 (<1%)	0	0	0
BRONCHOSPASM	1 (<1%)	0	1 (<1%)	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	0	1 (<1%)
DYSPNOEA	2 (<1%)	0	0	0
LARYNGITIS ALLERGIC	0	0	1 (<1%)	0
PULMONARY EMBOLISM	1 (<1%)	0	0	0
RESPIRATORY FAILURE	1 (<1%)	0	0	0
RHINITIS ALLERGIC	1 (<1%)	0	0	3 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	3 (<1%)	0	2 (<1%)	4 (<1%)
ACNE	1 (<1%)	0	0	0
ALOPECIA	0	0	0	1 (<1%)
ANGIOEDEMA	0	0	0	1 (<1%)
DERMATITIS	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 61

Summary of Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
...Continued from previous page				
SKIN & SUBCUTANEOUS TIS. DISORDERS				
DERMATITIS ALLERGIC	0	0	1 (<1%)	1 (<1%)
DERMATITIS CONTACT	0	0	1 (<1%)	0
PSORIASIS	1 (<1%)	0	0	0
URTICARIA	0	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	3 (<1%)	3 (<1%)
HYSTERECTOMY	0	0	2 (<1%)	0
LIPOSUCTION	0	0	0	1 (<1%)
NEPHRECTOMY	0	0	1 (<1%)	0
ROTATOR CUFF REPAIR	1 (<1%)	0	0	0
SEPTOPLASTY	0	0	0	1 (<1%)
UMBILICAL HERNIA REPAIR	0	0	0	1 (<1%)
VASCULAR DISORDERS	5 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)
CIRCULATORY COLLAPSE	0	1 (<1%)	0	0
DEEP VEIN THROMBOSIS	0	0	1 (<1%)	0
HOT FLUSH	1 (<1%)	0	0	0
HYPERTENSION	4 (<1%)	0	0	2 (<1%)
HYPERTENSIVE CRISIS	0	0	1 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 62

Summary of Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing Across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)
ANY ADVERSE EVENT	0	0	3 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	0	1 (<1%)	0
MALAISE	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	0	1 (<1%)	0
SYNOVIAL CYST	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	0	0	1 (<1%)	1 (<1%)
FACIAL PALSY	0	0	0	1 (<1%)
HEADACHE	0	0	1 (<1%)	0
PREG., PUERPERIUM & PERINATAL COND.	0	0	1 (<1%)	0
ABORTION SPONTANEOUS	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 63

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)
ANY ADVERSE EVENT	10 (1%)	2 (1%)	9 (1%)	7 (1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	0	0	0
HYPOACUSIS	1 (<1%)	0	0	0
EYE DISORDERS	0	0	1 (<1%)	0
RETINAL DETACHMENT	0	0	1 (<1%)	0
GASTROINTESTINAL DISORDERS	1 (<1%)	0	0	0
NAUSEA	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	3 (<1%)	0	4 (<1%)	1 (<1%)
APPENDICITIS	0	0	1 (<1%)	0
BRONCHITIS	0	0	1 (<1%)	0
CELLULITIS	0	0	0	1 (<1%)
KIDNEY INFECTION	1 (<1%)	0	0	0
MENINGITIS VIRAL	1 (<1%)	0	0	0
PNEUMONIA	2 (<1%)	0	2 (<1%)	0
INJURY & POISONING	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
ANKLE FRACTURE	0	0	0	1 (<1%)
BURNS SECOND DEGREE	0	1 (<1%)	0	0
MENISCUS LESION	0	0	0	1 (<1%)

Continued on next page...

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 63

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)
...Continued from previous page				
INJURY & POISONING				
OVERDOSE	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0	0	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	0	0	1 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
DYSTONIA	1 (<1%)	0	0	0
GRAND MAL CONVULSION	1 (<1%)	0	0	0
POST HERPETIC NEURALGIA	0	0	0	1 (<1%)
SYNCOPE	0	0	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)	0	0
TREMOR	0	0	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	0	0	2 (<1%)	0
ABORTION SPONTANEOUS	0	0	2 (<1%)	0
PSYCHIATRIC DISORDERS	2 (<1%)	0	0	0
DEPRESSION	1 (<1%)	0	0	0
SUICIDE ATTEMPT	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 63

Summary of Severe Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	P13 Menactra (N=334)	P17 ACWY (N=1579)	P17 Menactra (N=882)
RENAL & URINARY DISORDERS	0	1 (<1%)	0	1 (<1%)
NEPHROLITHIASIS	0	1 (<1%)	0	0
RENAL COLIC	0	0	0	1 (<1%)
RESP., THORACIC & MEDIASTINAL DIS.	2 (<1%)	0	0	0
PULMONARY EMBOLISM	1 (<1%)	0	0	0
RESPIRATORY FAILURE	1 (<1%)	0	0	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	1 (<1%)
URTICARIA	0	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	0	0
ROTATOR CUFF REPAIR	1 (<1%)	0	0	0
VASCULAR DISORDERS	0	1 (<1%)	0	0
CIRCULATORY COLLAPSE	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 64

Summary of Severe Probably or Possibly Related Treatment-emergent Adverse Events During Months 2 to 6, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1010)	 P13 Menactra (N=334)	 P17 ACWY (N=1579)	 P17 Menactra (N=882)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 65

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	P13 Menactra (N=336)	P17 ACWY (N=1588)	P17 Menactra (N=882)
ANY ADVERSE EVENT	246 (24%)	67 (20%)	382 (24%)	235 (27%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	4 (<1%)	1 (<1%)	11 (1%)	4 (<1%)
CARDIAC DISORDERS	1 (<1%)	0	0	4 (<1%)
EAR & LABYRINTH DISORDERS	2 (<1%)	1 (<1%)	7 (<1%)	7 (1%)
ENDOCRINE DISORDERS	1 (<1%)	0	1 (<1%)	3 (<1%)
EYE DISORDERS	5 (<1%)	0	5 (<1%)	5 (1%)
GASTROINTESTINAL DISORDERS	35 (3%)	12 (4%)	72 (5%)	43 (5%)
GEN. DISORDERS & ADMIN. SITE COND.	49 (5%)	9 (3%)	81 (5%)	30 (3%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	3 (<1%)	2 (1%)	1 (<1%)	0
INFECTIONS & INFESTATIONS	58 (6%)	18 (5%)	121 (8%)	71 (8%)
INJURY & POISONING	16 (2%)	6 (2%)	22 (1%)	16 (2%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 65

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
INVESTIGATIONS	5 (<1%)	1 (<1%)	0	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	6 (<1%)	3 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	48 (5%)	11 (3%)	55 (3%)	51 (6%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	2 (<1%)	0	5 (<1%)	2 (<1%)
NERVOUS SYSTEM DISORDERS	36 (4%)	12 (4%)	73 (5%)	52 (6%)
PREG., PUERPERIUM & PERINATAL COND.	0	0	4 (<1%)	0
PSYCHIATRIC DISORDERS	18 (2%)	3 (1%)	4 (<1%)	4 (<1%)
RENAL & URINARY DISORDERS	4 (<1%)	2 (1%)	1 (<1%)	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	10 (1%)	5 (1%)	17 (1%)	9 (1%)
RESP., THORACIC & MEDIASTINAL DIS.	37 (4%)	7 (2%)	21 (1%)	12 (1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	10 (1%)	4 (1%)	23 (1%)	18 (2%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0	3 (<1%)	3 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 65

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
VASCULAR DISORDERS	8 (1%)	3 (1%)	6 (<1%)	7 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 66

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
ANY ADVERSE EVENT	71 (7%)	17 (5%)	147 (9%)	80 (9%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	2 (<1%)	1 (<1%)	8 (1%)	1 (<1%)
EAR & LABYRINTH DISORDERS	0	1 (<1%)	6 (<1%)	4 (<1%)
EYE DISORDERS	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	10 (1%)	1 (<1%)	17 (1%)	14 (2%)
GEN. DISORDERS & ADMIN. SITE COND.	37 (4%)	6 (2%)	60 (4%)	20 (2%)
INFECTIONS & INFESTATIONS	4 (<1%)	1 (<1%)	23 (1%)	11 (1%)
INJURY & POISONING	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	0	0	0	2 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	11 (1%)	1 (<1%)	22 (1%)	15 (2%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	13 (1%)	3 (1%)	50 (3%)	29 (3%)
PREG., PUERPERIUM & PERINATAL COND.	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 66

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events, Comparing across Regions
US vs Latin America, Ages 19-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] P13 ACWY (N=1018)	 P13 Menactra (N=336)	 P17 ACWY (N=1588)	 P17 Menactra (N=882)
PSYCHIATRIC DISORDERS	4 (<1%)	0	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	0	0	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	5 (<1%)	2 (1%)	2 (<1%)	3 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	5 (<1%)	1 (<1%)	17 (1%)	9 (1%)
VASCULAR DISORDERS	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 67

Listing of Deaths

Site/Subject	Group	Study	- Death Information - Date of Death	Time of Death	Primary Cause of Death	Secondary Cause of Death	Reported by	Death Rel. Meningoc. Disease	Autopsy Performed?

None Reported

Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Men ACWY -	HEPATITIS (HEPATITIS, UNSPECIFIED)	15 (b) (6)	23 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (9,10,11, 99)	NOT RELATED
				OTHER ACTION TAKEN: LAB TESTS				
(b) (6)	Menomune	ABDOMINAL PAIN LOWER (RIGHT LOWER QUADRANT ABDOMINAL PAIN)	121 (b) (6)	7 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,4,8, 99)	NOT RELATED
				OTHER ACTION TAKEN: MD VISIT				
(b) (6)	Menomune	ARACHNOID CYST (CEREBELLAR ARACHNOID CYST)	104 (b) (6)	17 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (4,10,8)	NOT RELATED
(b) (6)	Menomune	WOUND INFECTION (WOUND INFECTION)	166 (b) (6)	12 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Menomune	HALLUCINATION, AUDITORY (COMMAND AUDITORY HALLUCINATIONS)	76* (b) (6)	65* (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
(b) (6)	Menomune	APPENDICITIS (APPENDICITIS)	90 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8,4)	NOT RELATED
(b) (6)	Men ACWY -	FEMUR FRACTURE (SALTER-HARRIS II FRACTURE DISTAL LEFT FEMUR)	39 (b) (6)	199 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (4,8,10, 11)	NOT RELATED

* = Calculation based on estimated date.
[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	TdaP	NEPHROLITHIASIS (RENAL CALCULOSIS)	30 (b) (6)	15 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	TdaPACWY	HEAT STROKE (HEAT STROKE)	50 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	TdaP	ABDOMINAL PAIN UPPER (EPIGASTRIC PAIN)	42 (b) (6)	37 (INTERM)	YES (MOD)	RECOVERED	NONE (10,8)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Sever- ity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Lot 1	ROAD TRAFFIC ACCIDENT (TRAUMA DUE TO MOTOR VEHICLE ACCIDENT)	50 (b) (6)	 (SGL/CONT)	YES (SEV)	AE PERSIST	NONE (10)	NOT RELATED
(b) (6)	Lot 3	MYOCLONIC EPILEPSY (JUVENILE MYOCLONIC EPILEPSY)	35 (b) (6)	<1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8,99)	NOT RELATED
				OTHER ACTION TAKEN: EMERGENCY ROOM VISIT				
(b) (6)	Lot 3	MULTIPLE DRUG OVERDOSE INTENTIONAL (INTENTIONAL INGESTION OF MULTIPLE MEDICATIONS)	1 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (11,10,99)	NOT RELATED
				OTHER ACTION TAKEN: WITHDRAWN PSYCHIATRIC CONSULT IV FLUIDS				
(b) (6)	Lot 2	INTENTIONAL OVERDOSE (NON LETHAL IBUPROFEN OVERDOSE)	57 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (99,11)	NOT RELATED
				OTHER ACTION TAKEN: ER VISIT				
(b) (6)	Lot 3	APPENDICITIS (GANGRENOUS APPENDICITIS)	147 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,11,8, 99)	NOT RELATED
				OTHER ACTION TAKEN: ANESTHESIA				
(b) (6)	Menactra	THERAPEUTIC AGENT TOXICITY (SALICYLATE TOXICITY)	120 (b) (6)	1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,11)	NOT RELATED
(b) (6)	Lot 1	SIMPLE PARTIAL SEIZURES (SIMPLE PARTIAL SEIZURE)	21 (b) (6)	5 (INTERM)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
(b) (6)	Lot 3	VITELLO-INTESTINAL DUCT REMNANT (MECKEL'S DIVERTICULUM)	21 (b) (6)	3 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8,11,4, 10)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Study: V59P13

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Lot 1	DEPRESSION SUICIDAL (DEPRESSION WITH SUICIDAL IDEATION)	10 (b) (6)	6 (SGL/CONT)	YES (SEV)	ALIVE W/SEQ	NONE (10)	NOT RELATED
(b) (6)	Lot 1	ROAD TRAFFIC ACCIDENT (ALL TERRAIN VEHICULAR ACCIDENT WITH TRAUMA)	159 (b) (6)	4 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Lot 1	MENINGITIS VIRAL (VIRAL MENINGITIS)	107 (b) (6)	23 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10,9)	NOT RELATED
		PNEUMONIA (PNEUMONIAE)	108 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10,9)	NOT RELATED
(b) (6)	Menactra	INTERVERTEBRAL DISC PROTRUSION (HERNIATED C5-C6)	10 (b) (6)	 (INTERM)	YES (SEV)	AE PERSIST	NONE (4,8,10)	NOT RELATED
(b) (6)	Lot 3	EPILEPSY (PRIMARY GENERALIZED IDIOPATHIC EPILEPSY)	151 (b) (6)	3 (SGL/CONT) OTHER ACTION TAKEN: MRI, EEG	YES (MOD)	ALIVE W/SEQ	NONE (4,99)	NOT RELATED
(b) (6)	Menactra	BURNS SECOND DEGREE (2ND DEGREE BURNS TO RIGHT ARM)	43 (b) (6)	28 (SGL/CONT)	YES (SEV)	ALIVE W/SEQ	NONE (10)	NOT RELATED
		CIRCULATORY COLLAPSE (COLLAPSE)	43 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
		SYNCOPE VASOVAGAL (VASOVAGAL SYNCOPE)	43 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Sever- ity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Lot 2	TONSILLITIS (TONSILLITIS)	113 (b) (6)	16 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Lot 2	EPIPHYSIOLYSIS (RIGHT HIP SLIPPED CAPITAL FEMORAL EPIPHYSIS)	102 (b) (6)	(SGL/CONT)	YES (SEV)	AE PERSIST	NONE (4,8,9,10, 99)	NOT RELATED
				OTHER ACTION TAKEN: MD CONSULTATION				
(b) (6)	Lot 2	PULMONARY EMBOLISM (PULMONARY EMBOLI)	158 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
(b) (6)	Lot 3	DYSTONIA (ACUTE DYSTONIC REACTION)	90 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,11,99)	NOT RELATED
				OTHER ACTION TAKEN: URGENT CARE VISIT				
(b) (6)	Menactra	FALL (TRAUMA TO RT. FIBULA + RT. ANKLE SECONDARY TO FALL)	16 (b) (6)	86 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
(b) (6)	Lot 3	CHEST PAIN (CHEST PAIN)	151 (b) (6)	1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,9,8)	NOT RELATED
(b) (6)	Lot 3	CLAVICLE FRACTURE (RIGHT CLAVICLE FRACTURE)	73 (b) (6)	1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Lot 3	SUICIDE ATTEMPT (SUICIDE ATTEMPT)	111 (b) (6)	4 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED

Continued on next page...

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
...Continued from previous page								
(b) (6)	Lot 3	ACCIDENTAL OVERDOSE (ACCIDENTAL OVERDOSE OF LITHIUM)	133 (b) (6)	1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
		SUICIDE ATTEMPT (SUICIDE ATTEMPT)	148 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
		SUICIDE ATTEMPT (SUICIDE ATTEMPT)	156 (b) (6)	14 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
(b) (6)	Lot 3	TRAUMATIC BRAIN INJURY (SEVERE CLOSED HEAD INJURY)	117 (b) (6)	10 (SGL/CONT)	YES (SEV)	ALIVE W/SEQ	NONE (10,8)	NOT RELATED
(b) (6)	Menactra	DISLOCATION OF STERNUM (STERNOMANUBRIUM DISLOCATION)	68 (b) (6)	2 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
		SPINAL COMPRESSION FRACTURE (T5 COMPRESSION FRACTURE)	68 (b) (6)	2 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Lot 1	LIGAMENT RUPTURE (RIGHT KNEE ANTERIOR CRUCIATE LIGAMENT TEAR)	141 (b) (6)	1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
		HYPOAESTHESIA (RIGHT FOOT NUMBNESS STATUS POST RIGHT ACL SURGERY)	142 (b) (6)	1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Lot 2	STAPHYLOCOCCAL INFECTION (RIGHT LEG ABCESS WITH METHICILLIN RESISTANT STAPH AUREUS)	72 (b) (6)	1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8,11, 99)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAE.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAE

Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Lot 3	ROAD TRAFFIC ACCIDENT (LEG TRAUMA POST MOTOR VEHICLE ACCIDENT)	164 (b) (6)	<1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10)	NOT RELATED
(b) (6)	Lot 1	OVERDOSE (DRUG OVERDOSE)	121 (b) (6)	5 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
		RESPIRATORY FAILURE (RESPIRATORY FAILURE)	121 (b) (6)	5 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
		SUICIDE ATTEMPT (SUICIDE ATTEMPT)	121 (b) (6)	9 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAE.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAE

Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Menactra	ANKLE FRACTURE (DISLOCATION FRACTURE OF RIGHT ANKLE)	124 (b) (6)	49 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,4,8)	NOT RELATED
(b) (6)	Menactra	ANGIOEDEMA (ANGIOEDEMA)	3 (b) (6)	1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (8,10)	NOT RELATED
(b) (6)	Menactra	HERPES ZOSTER (HERPES ZOSTER)	28 (b) (6)	13 (SGL/CONT)	YES (SEV) OTHER ACTION TAKEN: PHYSICIAN VISIT	RECOVERED	NONE (8,99)	NOT RELATED
		HIV INFECTION (HIV)	37 (b) (6)	(SGL/CONT)	YES (MILD)	AE PERSIST	NONE (8)	NOT RELATED
(b) (6)	ACWY	ABORTION SPONTANEOUS (SPONTANEOUS ABORTION)	141 (b) (6)	<1 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (4)	NOT RELATED
(b) (6)	ACWY	SYNCOPE (SYNCOPE)	64 (b) (6)	8 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (4,10)	NOT RELATED
(b) (6)	Menactra	INTERVERTEBRAL DISC PROTRUSION (LUMBAR DISC HERNIATION)	70 (b) (6)	13 (SGL/CONT)	YES (SEV)	ALIVE W/SEQ	NONE (10,8)	NOT RELATED
(b) (6)	ACWY	APPENDICITIS (GANGRENOUS APPENDICITIS)	95 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (4,10,8)	NOT RELATED
(b) (6)	ACWY	DEEP VEIN THROMBOSIS (RIGHT DEEP VEIN THROMBOSIS)	35 (b) (6)	15 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8,10)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Sever- ity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	ACWY	NEPHRECTOMY (NEPHRECTOMY)	116 (b) (6)	2 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	ACWY	PELVIC INFLAMMATORY DISEASE (INFLAMMATORY PELVIC DISEASE)	3 (b) (6)	12 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8,11)	NOT RELATED
(b) (6)	ACWY	ABORTION SPONTANEOUS (COMPLETE SPONTANEOUS ABORTION)	110 (b) (6)	4 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (99)	NOT RELATED
				OTHER ACTION TAKEN: VISIT TO PHYSICIAN				
(b) (6)	Menactra	ABDOMINAL PAIN (ABDOMINAL PAIN)	71 (b) (6)	1 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8,11)	NOT RELATED
(b) (6)	ACWY	ARTHROPOD STING (EDEMA CAUSED BY WASP STING)	114 (b) (6)	4 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8)	NOT RELATED
(b) (6)	ACWY	UPPER LIMB FRACTURE (OPEN ELBOW FRACTURE)	101 (b) (6)	3 (SGL/CONT)	YES (SEV)	ALIVE W/SEQ	NONE (10,11,99, 4,8)	NOT RELATED
				OTHER ACTION TAKEN: SURGERY PHYSICAL THERAPY				
(b) (6)	ACWY	HAEMATURIA (HEMATURIA)	77 (b) (6)	8 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8,10,11)	NOT RELATED
(b) (6)	Menactra	CELLULITIS (FACIAL CELLULITIS)	128 (b) (6)	9 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (8,10,11)	NOT RELATED
(b) (6)	Menactra	URTICARIA (URTICARIA)	108 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (11,8,10)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAE.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAE

Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	ACWY	ABORTION SPONTANEOUS (COMPLETE SPONTANEOUS ABORTION)	44 (b) (6)	3 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (99) OTHER ACTION TAKEN: ER VISIT, BLOOD BHCG AND ULTRASOUND	POSSIBLY RELATED
(b) (6)	Menactra	GENERALISED OEDEMA (EDEMA GENERALIZED)	30* (b) (6)	<1 - 29 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8)	NOT RELATED
		GENERALISED OEDEMA (EDEMA GENERALIZED)	60* (b) (6)	<1 - 30 (SGL/CONT)	YES (MOD)	RECOVERED	NONE (10,8)	NOT RELATED

* = Calculation based on estimated date.
[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

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Table 68

Listing of Serious Treatment-emergent Adverse Events

Site/ Subject	Group	MedDRA Preferred Term (Verbatim Term)	Onset Study Day (Date)	Duration Days (Freq.)	Serious (Severity)	Outcome	Action Taken Agent (Other[1])	Relationship
(b) (6)	Group II	ABORTION SPONTANEOUS (SPONTANEOUS ABORTION)	186 (b) (6)	7 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10)	NOT RELATED
(b) (6)	Group II	APPENDICITIS (ACUTE APPENDICITIS)	55 (b) (6)	3 (SGL/CONT)	YES (SEV)	RECOVERED	NONE (10,8)	NOT RELATED
(b) (6)	Group I	CUSHING'S SYNDROME (CUSHING'S SYNDROME)	16 (b) (6)	(SGL/CONT)	YES (MOD)	AE PERSIST	NO VACC DUE T (10,8,6)	NOT RELATED
		PITUITARY TUMOUR BENIGN (HYPOPHYSEAL MICROADENOMA)	16 (b) (6)	59 (SGL/CONT)	YES (MILD)	RECOVERED	NO VACC DUE T (10,6)	NOT RELATED

[1]2 = Uncertain, 4 = Procedure or physical therapy, 5 = Blood or blood products, 6 = Withdrawn from study due to AE, 8 = Prescription drug therapy, 9 = Non-prescription drug therapy, 10 = Hospitalization, 11 = IV Fluids, 99 = Other.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAE.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAE

Table 69

Summary of Serious Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY SERIOUS ADVERSE EVENT	22 (1%)	11 (1%)	7 (<1%)	40 (1%)	13 (1%)
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	0	1 (<1%)	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	0	1 (<1%)	0
ENDOCRINE DISORDERS	1 (<1%)	0	0	1 (<1%)	0
CUSHING'S SYNDROME	1 (<1%)	0	0	1 (<1%)	0
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (<1%)
ABDOMINAL PAIN	0	0	0	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CHEST PAIN	0	0	1 (<1%)	1 (<1%)	0
GENERALISED OEDEMA	0	0	0	0	1 (<1%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0	0	1 (<1%)	0
HEPATITIS	1 (<1%)	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	4 (<1%)	2 (<1%)	1 (<1%)	7 (<1%)	2 (<1%)
APPENDICITIS	2 (<1%)	1 (<1%)	0	3 (<1%)	0
CELLULITIS	0	0	0	0	1 (<1%)
HERPES ZOSTER	0	0	0	0	1 (<1%)
HIV INFECTION	0	0	0	0	1 (<1%)
MENINGITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_ACWY.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAESUM_ACWY

Table 69

Summary of Serious Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INFECTIONS & INFESTATIONS					
PELVIC INFLAMMATORY DISEASE	0	1 (<1%)	0	1 (<1%)	0
PNEUMONIA	0	0	1 (<1%)	1 (<1%)	0
STAPHYLOCOCCAL INFECTION	1 (<1%)	0	0	1 (<1%)	0
TONSILLITIS	1 (<1%)	0	0	1 (<1%)	0
INJURY & POISONING	10 (<1%)	3 (<1%)	1 (<1%)	14 (<1%)	5 (<1%)
ACCIDENTAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
ANKLE FRACTURE	0	0	0	0	1 (<1%)
ARTHROPOD STING	0	1 (<1%)	0	1 (<1%)	0
BURNS SECOND DEGREE	0	0	0	0	1 (<1%)
CLAVICLE FRACTURE	1 (<1%)	0	0	1 (<1%)	0
DISLOCATION OF STERNUM	0	0	0	0	1 (<1%)
FALL	0	0	0	0	1 (<1%)
FEMUR FRACTURE	1 (<1%)	0	0	1 (<1%)	0
HEAT STROKE	1 (<1%)	0	0	1 (<1%)	0
INTENTIONAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
LIGAMENT RUPTURE	1 (<1%)	0	0	1 (<1%)	0
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	0	1 (<1%)	0
OVERDOSE	0	1 (<1%)	0	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	1 (<1%)	0	3 (<1%)	0
SPINAL COMPRESSION FRACTURE	0	0	0	0	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_ACWY.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - SERAESUM_ACWY

Table 69

Summary of Serious Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
INJURY & POISONING					
THERAPEUTIC AGENT TOXICITY	0	0	0	0	1 (<1%)
TRAUMATIC BRAIN INJURY	1 (<1%)	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	0	1 (<1%)	2 (<1%)
EPIPHYSIOLYSIS	1 (<1%)	0	0	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	2 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0	0	1 (<1%)	0
PITUITARY TUMOUR BENIGN	1 (<1%)	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	3 (<1%)	1 (<1%)	2 (<1%)	6 (<1%)	1 (<1%)
DYSTONIA	0	1 (<1%)	0	1 (<1%)	0
EPILEPSY	0	0	1 (<1%)	1 (<1%)	0
HYPOAESTHESIA	1 (<1%)	0	0	1 (<1%)	0
MYOCLONIC EPILEPSY	1 (<1%)	0	0	1 (<1%)	0
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	0	1 (<1%)	0
SYNCOPE	0	0	1 (<1%)	1 (<1%)	0
SYNCOPE VASOVAGAL	0	0	0	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	3 (<1%)	0	4 (<1%)	0
ABORTION SPONTANEOUS	1 (<1%)	3 (<1%)	0	4 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

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Table 69

Summary of Serious Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
PSYCHIATRIC DISORDERS	2 (<1%)	1 (<1%)	0	3 (<1%)	0
DEPRESSION SUICIDAL	1 (<1%)	0	0	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RENAL & URINARY DISORDERS	0	0	1 (<1%)	1 (<1%)	0
HAEMATURIA	0	0	1 (<1%)	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	0	2 (<1%)	0	2 (<1%)	0
PULMONARY EMBOLISM	0	1 (<1%)	0	1 (<1%)	0
RESPIRATORY FAILURE	0	1 (<1%)	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	0	2 (<1%)
ANGIOEDEMA	0	0	0	0	1 (<1%)
URTICARIA	0	0	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	0	1 (<1%)	0	1 (<1%)	0
NEPHRECTOMY	0	1 (<1%)	0	1 (<1%)	0
VASCULAR DISORDERS	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CIRCULATORY COLLAPSE	0	0	0	0	1 (<1%)
DEEP VEIN THROMBOSIS	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

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Table 70.1

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	ACWYConVax (N=899)	Total ACWY (N=3579)	Menactra (N=539)	Menomune (N=209)	Tdap (N=892)
ANY SERIOUS ADVERSE EVENT	20 (1%)	2 (<1%)	22 (1%)	2 (<1%)	5 (2%)	2 (<1%)
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	1 (<1%)	0	0	0
ENDOCRINE DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
CUSHING'S SYNDROME	0	1 (<1%)	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (<1%)	1 (<1%)
ABDOMINAL PAIN LOWER	0	0	0	0	1 (<1%)	0
ABDOMINAL PAIN UPPER	0	0	0	0	0	1 (<1%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
HEPATITIS	1 (<1%)	0	1 (<1%)	0	0	0
INFECTIONS & INFESTATIONS	4 (<1%)	0	4 (<1%)	0	2 (1%)	0
APPENDICITIS	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0
STAPHYLOCOCCAL INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
TONSILLITIS	1 (<1%)	0	1 (<1%)	0	0	0
WOUND INFECTION	0	0	0	0	1 (<1%)	0
INJURY & POISONING	9 (<1%)	1 (<1%)	10 (<1%)	2 (<1%)	0	0
ACCIDENTAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_TRT_11_18.SAS(WARTERO) 10JUL08, 09:00 SAS.9.1 - SERAESUM_TRT_11_18

Table 70.1

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
INJURY & POISONING						
CLAVICLE FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
DISLOCATION OF STERNUM	0	0	0	1 (<1%)	0	0
FEMUR FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
HEAT STROKE	0	1 (<1%)	1 (<1%)	0	0	0
INTENTIONAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
LIGAMENT RUPTURE	1 (<1%)	0	1 (<1%)	0	0	0
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	0	2 (<1%)	0	0	0
SPINAL COMPRESSION FRACTURE	0	0	0	1 (<1%)	0	0
THERAPEUTIC AGENT TOXICITY	0	0	0	1 (<1%)	0	0
TRAUMATIC BRAIN INJURY	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	1 (<1%)	0	0	0
EPIPHYSIOLYSIS	1 (<1%)	0	1 (<1%)	0	0	0
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	1 (<1%)	1 (<1%)	0	0	0
PITUITARY TUMOUR BENIGN	0	1 (<1%)	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	3 (<1%)	0	3 (<1%)	0	1 (<1%)	0
ARACHNOID CYST	0	0	0	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 70.1

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
...Continued from previous page						
NERVOUS SYSTEM DISORDERS						
HYPOAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0
MYOCLONIC EPILEPSY	1 (<1%)	0	1 (<1%)	0	0	0
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	1 (<1%)	0	0	0
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	0	1 (<1%)	0	0	0
ABORTION SPONTANEOUS	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0
DEPRESSION SUICIDAL	1 (<1%)	0	1 (<1%)	0	0	0
HALLUCINATION, AUDITORY	0	0	0	0	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	0	1 (<1%)	0	0	0
RENAL & URINARY DISORDERS	0	0	0	0	0	1 (<1%)
NEPHROLITHIASIS	0	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 70.2

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY SERIOUS ADVERSE EVENT	11 (1%)	6 (1%)
GASTROINTESTINAL DISORDERS	0	1 (<1%)
ABDOMINAL PAIN	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	1 (<1%)
GENERALISED OEDEMA	0	1 (<1%)
INFECTIONS & INFESTATIONS	2 (<1%)	1 (<1%)
APPENDICITIS	1 (<1%)	0
CELLULITIS	0	1 (<1%)
PELVIC INFLAMMATORY DISEASE	1 (<1%)	0
INJURY & POISONING	3 (<1%)	2 (<1%)
ARTHROPOD STING	1 (<1%)	0
BURNS SECOND DEGREE	0	1 (<1%)
FALL	0	1 (<1%)
OVERDOSE	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)
DYSTONIA	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	3 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_TRT_19_34.SAS(WARTERO) 10JUL08, 09:00 SAS.9.1 - SERAESUM_TRT_19_34

Table 70.2

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
...Continued from previous page		
PREG., PUERPERIUM & PERINATAL COND.		
ABORTION SPONTANEOUS	3 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	2 (<1%)	0
PULMONARY EMBOLISM	1 (<1%)	0
RESPIRATORY FAILURE	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)
ANGIOEDEMA	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0
NEPHRECTOMY	1 (<1%)	0
VASCULAR DISORDERS	0	1 (<1%)
CIRCULATORY COLLAPSE	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

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Table 70.3

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY SERIOUS ADVERSE EVENT	7 (<1%)	5 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	1 (<1%)	0
CHEST PAIN	1 (<1%)	0
INFECTIONS & INFESTATIONS	1 (<1%)	1 (<1%)
HERPES ZOSTER	0	1 (<1%)
HIV INFECTION	0	1 (<1%)
MENINGITIS VIRAL	1 (<1%)	0
PNEUMONIA	1 (<1%)	0
INJURY & POISONING	1 (<1%)	1 (<1%)
ANKLE FRACTURE	0	1 (<1%)
UPPER LIMB FRACTURE	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	2 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	2 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	0
EPILEPSY	1 (<1%)	0
SYNCOPE	1 (<1%)	0
RENAL & URINARY DISORDERS	1 (<1%)	0
HAEMATURIA	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_TRT_35_55.SAS(WARTERO) 10JUL08, 09:01 SAS.9.1 - SERAESUM_TRT_35_55

Table 70.3

Summary of Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)
URTICARIA	0	1 (<1%)
VASCULAR DISORDERS	1 (<1%)	0
DEEP VEIN THROMBOSIS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\SERAESUM_TRT_35_55.SAS(WARTERO) 10JUL08, 09:01 SAS.9.1 - SERAESUM_TRT_35_55

Table 71

Summary of Serious Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY SERIOUS ADVERSE EVENT	6 (<1%)	1 (<1%)	0	7 (<1%)	4 (<1%)
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	0	1 (<1%)	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	0	1 (<1%)	0
ENDOCRINE DISORDERS	1 (<1%)	0	0	1 (<1%)	0
CUSHING'S SYNDROME	1 (<1%)	0	0	1 (<1%)	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0	0	1 (<1%)	0
HEPATITIS	1 (<1%)	0	0	1 (<1%)	0
INFECTIONS & INFESTATIONS	0	1 (<1%)	0	1 (<1%)	1 (<1%)
HERPES ZOSTER	0	0	0	0	1 (<1%)
PELVIC INFLAMMATORY DISEASE	0	1 (<1%)	0	1 (<1%)	0
INJURY & POISONING	1 (<1%)	0	0	1 (<1%)	1 (<1%)
FALL	0	0	0	0	1 (<1%)
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	0	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	0	0	0	1 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (<1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0	0	1 (<1%)	0
PITUITARY TUMOUR BENIGN	1 (<1%)	0	0	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	0	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - SERAESUM_ACWY_M1

Table 71

Summary of Serious Treatment-emergent Adverse Events During Month 1, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
...Continued from previous page					
NERVOUS SYSTEM DISORDERS					
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	0	1 (<1%)	0
DEPRESSION SUICIDAL	1 (<1%)	0	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	0	1 (<1%)
ANGIOEDEMA	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M1.SAS(WARTERO) 10JUL08, 08:20 SAS.9.1 - SERAESUM_ACWY_M1

Table 72.1

Summary of Serious Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY SERIOUS ADVERSE EVENT	5 (<1%)	1 (<1%)	6 (<1%)	0	0	0
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
VITELLO-INTESTINAL DUCT REMNANT	1 (<1%)	0	1 (<1%)	0	0	0
ENDOCRINE DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
CUSHING'S SYNDROME	0	1 (<1%)	1 (<1%)	0	0	0
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
HEPATITIS	1 (<1%)	0	1 (<1%)	0	0	0
INJURY & POISONING	1 (<1%)	0	1 (<1%)	0	0	0
MULTIPLE DRUG OVERDOSE INTENTIONAL	1 (<1%)	0	1 (<1%)	0	0	0
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	1 (<1%)	1 (<1%)	0	0	0
PITUITARY TUMOUR BENIGN	0	1 (<1%)	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
SIMPLE PARTIAL SEIZURES	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
DEPRESSION SUICIDAL	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M1_11_18.SAS(WARTERO) 10JUL08, 08:28 SAS.9.1 - SERAESUM_TRT_M1_11_18

Table 72.2

Summary of Serious Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY SERIOUS ADVERSE EVENT	1 (<1%)	2 (<1%)
INFECTIONS & INFESTATIONS	1 (<1%)	0
PELVIC INFLAMMATORY DISEASE	1 (<1%)	0
INJURY & POISONING	0	1 (<1%)
FALL	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)
ANGIOEDEMA	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M1_19_34.SAS(WARTERO) 10JUL08, 08:28 SAS.9.1 - SERAESUM_TRT_M1_19_34

Table 72.3

Summary of Serious Treatment-emergent Adverse Events During Month 1, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY SERIOUS ADVERSE EVENT	0	2 (<1%)
INFECTIONS & INFESTATIONS	0	1 (<1%)
HERPES ZOSTER	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	0	1 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M1_35_55.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - SERAESUM_TRT_M1_35_55

Table 73

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	 Ages 19-34 (N=1132)	 Ages 35-55 (N=1457)	 Total ACWY (N=5068)	 Total Menactra (N=1746)
ANY SERIOUS ADVERSE EVENT	14 (1%)	10 (1%)	7 (<1%)	31 (1%)	10 (1%)
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (<1%)
ABDOMINAL PAIN	0	0	0	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CHEST PAIN	0	0	1 (<1%)	1 (<1%)	0
GENERALISED OEDEMA	0	0	0	0	1 (<1%)
INFECTIONS & INFESTATIONS	3 (<1%)	1 (<1%)	1 (<1%)	5 (<1%)	2 (<1%)
APPENDICITIS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
CELLULITIS	0	0	0	0	1 (<1%)
HIV INFECTION	0	0	0	0	1 (<1%)
MENINGITIS VIRAL	0	0	1 (<1%)	1 (<1%)	0
PNEUMONIA	0	0	1 (<1%)	1 (<1%)	0
STAPHYLOCOCCAL INFECTION	1 (<1%)	0	0	1 (<1%)	0
TONSILLITIS	1 (<1%)	0	0	1 (<1%)	0
INJURY & POISONING	9 (<1%)	3 (<1%)	1 (<1%)	13 (<1%)	4 (<1%)
ACCIDENTAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
ANKLE FRACTURE	0	0	0	0	1 (<1%)
ARTHROPOD STING	0	1 (<1%)	0	1 (<1%)	0

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - SERAESUM_ACWY_M26

Table 73

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
INJURY & POISONING					
BURNS SECOND DEGREE	0	0	0	0	1 (<1%)
CLAVICLE FRACTURE	1 (<1%)	0	0	1 (<1%)	0
DISLOCATION OF STERNUM	0	0	0	0	1 (<1%)
FEMUR FRACTURE	1 (<1%)	0	0	1 (<1%)	0
HEAT STROKE	1 (<1%)	0	0	1 (<1%)	0
INTENTIONAL OVERDOSE	1 (<1%)	0	0	1 (<1%)	0
LIGAMENT RUPTURE	1 (<1%)	0	0	1 (<1%)	0
OVERDOSE	0	1 (<1%)	0	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	1 (<1%)	0	3 (<1%)	0
SPINAL COMPRESSION FRACTURE	0	0	0	0	1 (<1%)
THERAPEUTIC AGENT TOXICITY	0	0	0	0	1 (<1%)
TRAUMATIC BRAIN INJURY	1 (<1%)	0	0	1 (<1%)	0
UPPER LIMB FRACTURE	0	0	1 (<1%)	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	0	1 (<1%)	1 (<1%)
EPIPHYSIOLYSIS	1 (<1%)	0	0	1 (<1%)	0
INTERVERTEBRAL DISC PROTRUSION	0	0	0	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	1 (<1%)	2 (<1%)	5 (<1%)	1 (<1%)

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[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - SERAESUM_ACWY_M26

Table 73

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
NERVOUS SYSTEM DISORDERS					
DYSTONIA	0	1 (<1%)	0	1 (<1%)	0
EPILEPSY	0	0	1 (<1%)	1 (<1%)	0
HYPOAESTHESIA	1 (<1%)	0	0	1 (<1%)	0
MYOCLONIC EPILEPSY	1 (<1%)	0	0	1 (<1%)	0
SYNCOPE	0	0	1 (<1%)	1 (<1%)	0
SYNCOPE VASOVAGAL	0	0	0	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	0	3 (<1%)	0	3 (<1%)	0
ABORTION SPONTANEOUS	0	3 (<1%)	0	3 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RENAL & URINARY DISORDERS	0	0	1 (<1%)	1 (<1%)	0
HAEMATURIA	0	0	1 (<1%)	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	0	2 (<1%)	0	2 (<1%)	0
PULMONARY EMBOLISM	0	1 (<1%)	0	1 (<1%)	0
RESPIRATORY FAILURE	0	1 (<1%)	0	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - SERAESUM_ACWY_M26

Table 73

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Total MenACWY[1] across Age Groups
(Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=2479)	Ages 19-34 (N=1132)	Ages 35-55 (N=1457)	Total ACWY (N=5068)	Total Menactra (N=1746)
...Continued from previous page					
SKIN & SUBCUTANEOUS TIS. DISORDERS					
URTICARIA	0	0	0	0	1 (<1%)
SURGICAL & MEDICAL PROCEDURES	0	1 (<1%)	0	1 (<1%)	0
NEPHRECTOMY	0	1 (<1%)	0	1 (<1%)	0
VASCULAR DISORDERS	0	0	1 (<1%)	1 (<1%)	1 (<1%)
CIRCULATORY COLLAPSE	0	0	0	0	1 (<1%)
DEEP VEIN THROMBOSIS	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_ACWY_M26.SAS(WARTERO) 10JUL08, 08:21 SAS.9.1 - SERAESUM_ACWY_M26

Table 74.1

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	ACWYConVax (N=359)	Total ACWY (N=2498)	Menactra (N=539)	Menomune (N=209)	Tdap (N=353)
ANY SERIOUS ADVERSE EVENT	13 (1%)	1 (<1%)	14 (1%)	2 (<1%)	5 (2%)	2 (1%)
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (<1%)	1 (<1%)
ABDOMINAL PAIN LOWER	0	0	0	0	1 (<1%)	0
ABDOMINAL PAIN UPPER	0	0	0	0	0	1 (<1%)
INFECTIONS & INFESTATIONS	3 (<1%)	0	3 (<1%)	0	2 (1%)	0
APPENDICITIS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
STAPHYLOCOCCAL INFECTION	1 (<1%)	0	1 (<1%)	0	0	0
TONSILLITIS	1 (<1%)	0	1 (<1%)	0	0	0
WOUND INFECTION	0	0	0	0	1 (<1%)	0
INJURY & POISONING	8 (<1%)	1 (<1%)	9 (<1%)	2 (<1%)	0	0
ACCIDENTAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
CLAVICLE FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
DISLOCATION OF STERNUM	0	0	0	1 (<1%)	0	0
FEMUR FRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
HEAT STROKE	0	1 (<1%)	1 (<1%)	0	0	0
INTENTIONAL OVERDOSE	1 (<1%)	0	1 (<1%)	0	0	0
LIGAMENT RUPTURE	1 (<1%)	0	1 (<1%)	0	0	0
ROAD TRAFFIC ACCIDENT	2 (<1%)	0	2 (<1%)	0	0	0
SPINAL COMPRESSION FRACTURE	0	0	0	1 (<1%)	0	0
THERAPEUTIC AGENT TOXICITY	0	0	0	1 (<1%)	0	0
TRAUMATIC BRAIN INJURY	1 (<1%)	0	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - SERAESUM_TRT_M26_11_18

Table 74.1

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 11-18 (Study V59P18 excluded)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2139)	 ACWYConVax (N=359)	 Total ACWY (N=2498)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=353)
MUSCULO., CONNECT. TIS. & BONE DIS.	1 (<1%)	0	1 (<1%)	0	0	0
EPIPHYSIOLYSIS	1 (<1%)	0	1 (<1%)	0	0	0
NERVOUS SYSTEM DISORDERS	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0
ARACHNOID CYST	0	0	0	0	1 (<1%)	0
HYPOAESTHESIA	1 (<1%)	0	1 (<1%)	0	0	0
MYOCLONIC EPILEPSY	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
HALLUCINATION, AUDITORY	0	0	0	0	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	0	1 (<1%)	0	0	0
RENAL & URINARY DISORDERS	0	0	0	0	0	1 (<1%)
NEPHROLITHIASIS	0	0	0	0	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_11_18.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - SERAESUM_TRT_M26_11_18

Table 74.2

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY SERIOUS ADVERSE EVENT	10 (1%)	4 (1%)
GASTROINTESTINAL DISORDERS	0	1 (<1%)
ABDOMINAL PAIN	0	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	0	1 (<1%)
GENERALISED OEDEMA	0	1 (<1%)
INFECTIONS & INFESTATIONS	1 (<1%)	1 (<1%)
APPENDICITIS	1 (<1%)	0
CELLULITIS	0	1 (<1%)
INJURY & POISONING	3 (<1%)	1 (<1%)
ARTHROPOD STING	1 (<1%)	0
BURNS SECOND DEGREE	0	1 (<1%)
OVERDOSE	1 (<1%)	0
ROAD TRAFFIC ACCIDENT	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	1 (<1%)	1 (<1%)
DYSTONIA	1 (<1%)	0
SYNCOPE VASOVAGAL	0	1 (<1%)
PREG., PUERPERIUM & PERINATAL COND.	3 (<1%)	0
ABORTION SPONTANEOUS	3 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - SERAESUM_TRT_M26_19_34

Table 74.2

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
PSYCHIATRIC DISORDERS	1 (<1%)	0
SUICIDE ATTEMPT	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	2 (<1%)	0
PULMONARY EMBOLISM	1 (<1%)	0
RESPIRATORY FAILURE	1 (<1%)	0
SURGICAL & MEDICAL PROCEDURES	1 (<1%)	0
NEPHRECTOMY	1 (<1%)	0
VASCULAR DISORDERS	0	1 (<1%)
CIRCULATORY COLLAPSE	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_19_34.SAS(WARTERO) 10JUL08, 08:29 SAS.9.1 - SERAESUM_TRT_M26_19_34

Table 74.3

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY SERIOUS ADVERSE EVENT	7 (<1%)	4 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	1 (<1%)	0
CHEST PAIN	1 (<1%)	0
INFECTIONS & INFESTATIONS	1 (<1%)	1 (<1%)
HIV INFECTION	0	1 (<1%)
MENINGITIS VIRAL	1 (<1%)	0
PNEUMONIA	1 (<1%)	0
INJURY & POISONING	1 (<1%)	1 (<1%)
ANKLE FRACTURE	0	1 (<1%)
UPPER LIMB FRACTURE	1 (<1%)	0
MUSCULO., CONNECT. TIS. & BONE DIS.	0	1 (<1%)
INTERVERTEBRAL DISC PROTRUSION	0	1 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	0
EPILEPSY	1 (<1%)	0
SYNCOPE	1 (<1%)	0
RENAL & URINARY DISORDERS	1 (<1%)	0
HAEMATURIA	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1 - SERAESUM_TRT_M26_35_55

Table 74.3

Summary of Serious Treatment-emergent Adverse Events During Months 2 to 6, Comparing Treatment within Age Group
Subjects ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
...Continued from previous page		
SKIN & SUBCUTANEOUS TIS. DISORDERS		
URTICARIA	0	1 (<1%)
VASCULAR DISORDERS	1 (<1%)	0
DEEP VEIN THROMBOSIS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AE_TRT_M26_35_55.SAS(WARTERO) 10JUL08, 08:30 SAS.9.1 - SERAESUM_TRT_M26_35_55

Table 75

Summary of Probably or Possibly Related Serious Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY SERIOUS ADVERSE EVENT	0	1 (<1%)	0	1 (<1%)	0
PREG., PUERPERIUM & PERINATAL COND.	0	1 (<1%)	0	1 (<1%)	0
ABORTION SPONTANEOUS	0	1 (<1%)	0	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRSERAESUM_ACWY.SAS(WARTERO) 10JUL08, 08:57 SAS.9.1 - PRSERAESUM_ACWY

Table 76.1

Summary of Probably or Possibly Related Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1]					
	ACWY (N=2680)	ACWYConVax (N=899)	Total ACWY (N=3579)	Menactra (N=539)	Menomune (N=209)	Tdap (N=892)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRSERAESUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:58 SAS.9.1 - PRSERAESUM_TRT_11_18

Agent: MenACWY

Table 76.2

Summary of Probably or Possibly Related Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY SERIOUS ADVERSE EVENT	1 (<1%)	0
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	0
ABORTION SPONTANEOUS	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRSERAESUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:58 SAS.9.1 - PRSERAESUM_TRT_19_34

Table 76.3

Summary of Probably or Possibly Related Serious Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)

None Reported

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRSERAESUM_TRT_35_55.SAS(WARTERO) 10JUL08, 08:59 SAS.9.1 - PRSERAESUM_TRT_35_55

Table 77

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	846 (24%)	259 (23%)	369 (25%)	1474 (24%)	443 (25%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	8 (<1%)	4 (<1%)	11 (1%)	23 (<1%)	5 (<1%)
CARDIAC DISORDERS	3 (<1%)	0	1 (<1%)	4 (<1%)	4 (<1%)
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	0	1 (<1%)	0
EAR & LABYRINTH DISORDERS	11 (<1%)	4 (<1%)	5 (<1%)	20 (<1%)	9 (1%)
ENDOCRINE DISORDERS	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
EYE DISORDERS	11 (<1%)	3 (<1%)	7 (<1%)	21 (<1%)	8 (<1%)
GASTROINTESTINAL DISORDERS	130 (4%)	58 (5%)	49 (3%)	237 (4%)	73 (4%)
GEN. DISORDERS & ADMIN. SITE COND.	123 (3%)	49 (4%)	81 (6%)	253 (4%)	54 (3%)
HEPATO-BILIARY DISORDERS	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	0
IMMUNE SYSTEM DISORDERS	9 (<1%)	2 (<1%)	2 (<1%)	13 (<1%)	3 (<1%)
INFECTIONS & INFESTATIONS	263 (7%)	80 (7%)	99 (7%)	442 (7%)	121 (7%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_ACWY.SAS(WARTERO) 10JUL08, 08:13 SAS.9.1 - AESOCSUM_ACWY

Table 77

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
INJURY & POISONING	122 (3%)	17 (1%)	21 (1%)	160 (3%)	56 (3%)
INVESTIGATIONS	3 (<1%)	0	5 (<1%)	8 (<1%)	3 (<1%)
METABOLISM & NUTRITION DISORDERS	11 (<1%)	0	8 (1%)	19 (<1%)	5 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	73 (2%)	27 (2%)	76 (5%)	176 (3%)	81 (5%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	3 (<1%)	1 (<1%)	6 (<1%)	10 (<1%)	3 (<1%)
NERVOUS SYSTEM DISORDERS	107 (3%)	53 (5%)	56 (4%)	216 (3%)	84 (5%)
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	4 (<1%)	0	5 (<1%)	0
PSYCHIATRIC DISORDERS	28 (1%)	8 (1%)	14 (1%)	50 (1%)	16 (1%)
RENAL & URINARY DISORDERS	0	1 (<1%)	4 (<1%)	5 (<1%)	3 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	52 (1%)	16 (1%)	11 (1%)	79 (1%)	16 (1%)
RESP., THORACIC & MEDIASTINAL DIS.	113 (3%)	22 (2%)	36 (2%)	171 (3%)	38 (2%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	60 (2%)	11 (1%)	22 (2%)	93 (2%)	37 (2%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_ACWY.SAS(WARTERO) 10JUL08, 08:13 SAS.9.1 - AESOCSUM_ACWY

Table 77

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
SURGICAL & MEDICAL PROCEDURES	11 (<1%)	2 (<1%)	2 (<1%)	15 (<1%)	3 (<1%)
VASCULAR DISORDERS	0	1 (<1%)	13 (1%)	14 (<1%)	11 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_ACWY.SAS(WARTERO) 10JUL08, 08:13 SAS.9.1 - AESOCSUM_ACWY

Table 78.1

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	675 (25%)	171 (19%)	846 (24%)	141 (26%)	73 (35%)	157 (18%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	8 (<1%)	0	8 (<1%)	0	1 (<1%)	3 (<1%)
CARDIAC DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
CONGEN. & FAMIL./GENETIC DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	9 (<1%)	2 (<1%)	11 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
ENDOCRINE DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0
EYE DISORDERS	10 (<1%)	1 (<1%)	11 (<1%)	3 (1%)	2 (1%)	1 (<1%)
GASTROINTESTINAL DISORDERS	96 (4%)	34 (4%)	130 (4%)	18 (3%)	9 (4%)	30 (3%)
GEN. DISORDERS & ADMIN. SITE COND.	97 (4%)	26 (3%)	123 (3%)	15 (3%)	8 (4%)	26 (3%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
IMMUNE SYSTEM DISORDERS	6 (<1%)	3 (<1%)	9 (<1%)	1 (<1%)	3 (1%)	6 (1%)
INFECTIONS & INFESTATIONS	182 (7%)	81 (9%)	263 (7%)	32 (6%)	28 (13%)	57 (6%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:14 SAS.9.1 - AESOCSUM_TRT_11_18

Table 78.1

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
INJURY & POISONING	118 (4%)	4 (<1%)	122 (3%)	34 (6%)	13 (6%)	10 (1%)
INVESTIGATIONS	3 (<1%)	0	3 (<1%)	2 (<1%)	0	0
METABOLISM & NUTRITION DISORDERS	10 (<1%)	1 (<1%)	11 (<1%)	2 (<1%)	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	65 (2%)	8 (1%)	73 (2%)	19 (4%)	4 (2%)	15 (2%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	0	0
NERVOUS SYSTEM DISORDERS	82 (3%)	25 (3%)	107 (3%)	20 (4%)	15 (7%)	27 (3%)
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	0	1 (<1%)	0	0	0
PSYCHIATRIC DISORDERS	26 (1%)	2 (<1%)	28 (1%)	9 (2%)	5 (2%)	2 (<1%)
RENAL & URINARY DISORDERS	0	0	0	0	0	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	32 (1%)	20 (2%)	52 (1%)	2 (<1%)	3 (1%)	15 (2%)
RESP., THORACIC & MEDIASTINAL DIS.	99 (4%)	14 (2%)	113 (3%)	19 (4%)	16 (8%)	14 (2%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	51 (2%)	9 (1%)	60 (2%)	15 (3%)	2 (1%)	6 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:14 SAS.9.1 - AESOCSUM_TRT_11_18

Table 78.1

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
SURGICAL & MEDICAL PROCEDURES	8 (<1%)	3 (<1%)	11 (<1%)	0	0	2 (<1%)
VASCULAR DISORDERS	0	0	0	1 (<1%)	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:14 SAS.9.1 - AESOCSUM_TRT_11_18

Table 78.2

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	259 (23%)	128 (22%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	4 (<1%)	2 (<1%)
CARDIAC DISORDERS	0	2 (<1%)
EAR & LABYRINTH DISORDERS	4 (<1%)	3 (1%)
ENDOCRINE DISORDERS	1 (<1%)	0
EYE DISORDERS	3 (<1%)	1 (<1%)
GASTROINTESTINAL DISORDERS	58 (5%)	29 (5%)
GEN. DISORDERS & ADMIN. SITE COND.	49 (4%)	13 (2%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	2 (<1%)	2 (<1%)
INFECTIONS & INFESTATIONS	80 (7%)	41 (7%)
INJURY & POISONING	17 (1%)	13 (2%)
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:14 SAS.9.1 - AESOCSUM_TRT_19_34

Table 78.2

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
MUSCULO., CONNECT. TIS. & BONE DIS.	27 (2%)	20 (4%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	53 (5%)	25 (4%)
PREG., PUERPERIUM & PERINATAL COND.	4 (<1%)	0
PSYCHIATRIC DISORDERS	8 (1%)	5 (1%)
RENAL & URINARY DISORDERS	1 (<1%)	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	16 (1%)	5 (1%)
RESP., THORACIC & MEDIASTINAL DIS.	22 (2%)	10 (2%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	11 (1%)	10 (2%)
SURGICAL & MEDICAL PROCEDURES	2 (<1%)	3 (1%)
VASCULAR DISORDERS	1 (<1%)	3 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:14 SAS.9.1 - AESOCSUM_TRT_19_34

Table 78.3

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	369 (25%)	174 (27%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	11 (1%)	3 (<1%)
CARDIAC DISORDERS	1 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	5 (<1%)	5 (1%)
ENDOCRINE DISORDERS	1 (<1%)	3 (<1%)
EYE DISORDERS	7 (<1%)	4 (1%)
GASTROINTESTINAL DISORDERS	49 (3%)	26 (4%)
GEN. DISORDERS & ADMIN. SITE COND.	81 (6%)	26 (4%)
HEPATO-BILIARY DISORDERS	1 (<1%)	0
IMMUNE SYSTEM DISORDERS	2 (<1%)	0
INFECTIONS & INFESTATIONS	99 (7%)	48 (7%)
INJURY & POISONING	21 (1%)	9 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_35_55.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESOCSUM_TRT_35_55

Table 78.3

Summary of System Organ Classes Affected by Treatment-emergent Adverse Events, Comparing Treatment within Age Group
Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
INVESTIGATIONS	5 (<1%)	1 (<1%)
METABOLISM & NUTRITION DISORDERS	8 (1%)	2 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	76 (5%)	42 (6%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	6 (<1%)	2 (<1%)
NERVOUS SYSTEM DISORDERS	56 (4%)	39 (6%)
PSYCHIATRIC DISORDERS	14 (1%)	2 (<1%)
RENAL & URINARY DISORDERS	4 (<1%)	2 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	11 (1%)	9 (1%)
RESP., THORACIC & MEDIASTINAL DIS.	36 (2%)	9 (1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	22 (2%)	12 (2%)
SURGICAL & MEDICAL PROCEDURES	2 (<1%)	0
VASCULAR DISORDERS	13 (1%)	7 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\AESOCSUM_TRT_35_55.SAS(WARTERO) 10JUL08, 08:15 SAS.9.1 - AESOCSUM_TRT_35_55

Table 79

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
ANY ADVERSE EVENT	147 (4%)	87 (8%)	131 (9%)	365 (6%)	130 (7%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	3 (<1%)	7 (<1%)	13 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	1 (<1%)	3 (<1%)	3 (<1%)	7 (<1%)	5 (<1%)
EYE DISORDERS	0	0	1 (<1%)	1 (<1%)	0
GASTROINTESTINAL DISORDERS	27 (1%)	18 (2%)	9 (1%)	54 (1%)	21 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	71 (2%)	32 (3%)	65 (4%)	168 (3%)	36 (2%)
INFECTIONS & INFESTATIONS	11 (<1%)	10 (1%)	17 (1%)	38 (1%)	14 (1%)
INJURY & POISONING	1 (<1%)	0	1 (<1%)	2 (<1%)	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	0	2 (<1%)	2 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	17 (<1%)	7 (1%)	26 (2%)	50 (1%)	21 (1%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	0	0	1 (<1%)	1 (<1%)	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_ACWY.SAS(WARTERO) 10JUL08, 08:53 SAS.9.1 - PRAESOCSUM_ACWY

Table 79

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Total MenACWY[1] across Age Groups

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] Ages 11-18 (N=3579)	Ages 19-34 (N=1145)	Ages 35-55 (N=1461)	Total ACWY (N=6185)	Total Menactra (N=1757)
NERVOUS SYSTEM DISORDERS	31 (1%)	33 (3%)	30 (2%)	94 (2%)	42 (2%)
PREG., PUERPERIUM & PERINATAL COND.	0	1 (<1%)	0	1 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)	3 (<1%)	5 (<1%)	2 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	1 (<1%)	0	2 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	8 (<1%)	0	7 (<1%)	15 (<1%)	8 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	10 (<1%)	6 (1%)	16 (1%)	32 (1%)	16 (1%)
VASCULAR DISORDERS	0	0	2 (<1%)	2 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.
[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_ACWY.SAS(WARTERO) 10JUL08, 08:53 SAS.9.1 - PRAESOCSUM_ACWY

Table 80.1

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
ANY ADVERSE EVENT	115 (4%)	32 (4%)	147 (4%)	33 (6%)	5 (2%)	36 (4%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	0	3 (<1%)	0	0	0
EAR & LABYRINTH DISORDERS	1 (<1%)	0	1 (<1%)	0	0	0
GASTROINTESTINAL DISORDERS	21 (1%)	6 (1%)	27 (1%)	6 (1%)	0	12 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	60 (2%)	11 (1%)	71 (2%)	10 (2%)	2 (1%)	16 (2%)
INFECTIONS & INFESTATIONS	6 (<1%)	5 (1%)	11 (<1%)	2 (<1%)	0	1 (<1%)
INJURY & POISONING	1 (<1%)	0	1 (<1%)	0	0	0
METABOLISM & NUTRITION DISORDERS	2 (<1%)	0	2 (<1%)	0	0	0
MUSCULO., CONNECT. TIS. & BONE DIS.	14 (1%)	3 (<1%)	17 (<1%)	5 (1%)	3 (1%)	9 (1%)
NERVOUS SYSTEM DISORDERS	19 (1%)	12 (1%)	31 (1%)	10 (2%)	0	15 (2%)
PSYCHIATRIC DISORDERS	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
REPRODUCT. SYS. & BREAST DISORDERS	0	1 (<1%)	1 (<1%)	0	0	0

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_11_18

Table 80.1

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 11-18

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=2680)	 ACWYConVax (N=899)	 Total ACWY (N=3579)	 Menactra (N=539)	 Menomune (N=209)	 Tdap (N=892)
RESP., THORACIC & MEDIASTINAL DIS.	8 (<1%)	0	8 (<1%)	3 (1%)	0	1 (<1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	8 (<1%)	2 (<1%)	10 (<1%)	6 (1%)	1 (<1%)	3 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_11_18.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_11_18

Table 80.2

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
ANY ADVERSE EVENT	87 (8%)	40 (7%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	3 (<1%)	2 (<1%)
EAR & LABYRINTH DISORDERS	3 (<1%)	2 (<1%)
GASTROINTESTINAL DISORDERS	18 (2%)	9 (2%)
GEN. DISORDERS & ADMIN. SITE COND.	32 (3%)	8 (1%)
INFECTIONS & INFESTATIONS	10 (1%)	6 (1%)
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	7 (1%)	5 (1%)
NERVOUS SYSTEM DISORDERS	33 (3%)	12 (2%)
PREG., PUERPERIUM & PERINATAL COND.	1 (<1%)	0
PSYCHIATRIC DISORDERS	1 (<1%)	1 (<1%)
REPRODUCT. SYS. & BREAST DISORDERS	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	0	1 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_19_34

Table 80.2

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 19-34

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1145)	 Menactra (N=569)
SKIN & SUBCUTANEOUS TIS. DISORDERS	6 (1%)	3 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_19_34.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_19_34

Table 80.3

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
ANY ADVERSE EVENT	131 (9%)	57 (9%)
BLOOD & LYMPHATIC SYSTEM DISORDERS	7 (<1%)	0
EAR & LABYRINTH DISORDERS	3 (<1%)	3 (<1%)
EYE DISORDERS	1 (<1%)	0
GASTROINTESTINAL DISORDERS	9 (1%)	6 (1%)
GEN. DISORDERS & ADMIN. SITE COND.	65 (4%)	18 (3%)
INFECTIONS & INFESTATIONS	17 (1%)	6 (1%)
INJURY & POISONING	1 (<1%)	0
METABOLISM & NUTRITION DISORDERS	0	1 (<1%)
MUSCULO., CONNECT. TIS. & BONE DIS.	26 (2%)	11 (2%)
NEO. BEN./MALIG.(INC. CYSTS/POLYPS)	1 (<1%)	0
NERVOUS SYSTEM DISORDERS	30 (2%)	20 (3%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_35_55.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_35_55

Table 80.3

Summary of System Organ Classes Affected by Probably or Possibly Related Treatment-emergent Adverse Events
Comparing Treatment within Age Group, Subjects Ages 35-55

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY (N=1461)	 Menactra (N=649)
PSYCHIATRIC DISORDERS	3 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	7 (<1%)	4 (1%)
SKIN & SUBCUTANEOUS TIS. DISORDERS	16 (1%)	7 (1%)
VASCULAR DISORDERS	2 (<1%)	2 (<1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PRAESOCSUM_TRT_35_55.SAS(WARTERO) 10JUL08, 08:54 SAS.9.1 - PRAESOCSUM_TRT_35_55

Table 81

Summary of Subjects With At Least One Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: FEMALE

Reaction		Number (%) of Subjects				
		Ages 11-18 (N=1795)	Ages 19-34 (N=771)	Ages 35-55 (N=1079)	Total ACWY (N=3645)	Total Menactra (N=1113)
Any	ANY	1306 (73%)	539 (70%)	659 (61%)	2504 (69%)	766 (69%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	486 (27%)	232 (30%)	420 (39%)	1138 (31%)	347 (31%)
Local	ANY	957 (53%)	430 (56%)	492 (46%)	1879 (52%)	609 (55%)
	MISSING	4 (<1%)	0	0	4 (<1%)	0
	NONE	834 (46%)	341 (44%)	587 (54%)	1762 (48%)	504 (45%)
Systemic	ANY	985 (55%)	357 (46%)	436 (40%)	1778 (49%)	510 (46%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	807 (45%)	414 (54%)	643 (60%)	1864 (51%)	603 (54%)
Other	ANY	378 (21%)	178 (23%)	249 (23%)	805 (22%)	253 (23%)
	MISSING	3 (<1%)	0	0	3 (<1%)	1 (<1%)
	NONE	1414 (79%)	593 (77%)	830 (77%)	2837 (78%)	859 (77%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJOVW_ACWY_SEX

Table 81

Summary of Subjects With At Least One Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: MALE

Reaction		Number (%) of Subjects				
		Ages 11-18 (N=1784)	Ages 19-34 (N=374)	Ages 35-55 (N=382)	Total ACWY (N=2540)	Total Menactra (N=644)
Any	ANY	1100 (62%)	204 (55%)	158 (41%)	1462 (58%)	380 (59%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	681 (38%)	170 (45%)	224 (59%)	1075 (42%)	264 (41%)
Local	ANY	782 (44%)	160 (43%)	113 (30%)	1055 (42%)	297 (46%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	999 (56%)	214 (57%)	269 (70%)	1482 (58%)	347 (54%)
Systemic	ANY	763 (43%)	103 (28%)	96 (25%)	962 (38%)	215 (33%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	1018 (57%)	271 (72%)	286 (75%)	1575 (62%)	429 (67%)
Other	ANY	279 (16%)	47 (13%)	49 (13%)	375 (15%)	92 (14%)
	MISSING	3 (<1%)	0	0	3 (<1%)	0
	NONE	1502 (84%)	327 (87%)	333 (87%)	2162 (85%)	552 (86%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJOVW_ACWY_SEX

Table 82

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=62)	P6 Menomune (N=81)	P11 ACWY (N=165)	P11 Tdap (N=163)	P13 ACWY (N=764)	P13 Menactra (N=250)	P18 ACWY (N=309)	P18 Tdap (N=307)
Any	ANY	53 (85%)	69 (85%)	116 (70%)	149 (91%)	537 (70%)	192 (77%)	223 (72%)	268 (87%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	9 (15%)	12 (15%)	49 (30%)	14 (9%)	224 (29%)	58 (23%)	86 (28%)	39 (13%)
Local	ANY	46 (74%)	58 (72%)	84 (51%)	130 (80%)	424 (55%)	159 (64%)	170 (55%)	245 (80%)
	MISSING	0	0	0	0	4 (1%)	0	0	0
	NONE	16 (26%)	23 (28%)	81 (49%)	33 (20%)	336 (44%)	91 (36%)	139 (45%)	62 (20%)
Systemic	ANY	38 (61%)	43 (53%)	94 (57%)	113 (69%)	382 (50%)	127 (51%)	161 (52%)	191 (62%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	24 (39%)	38 (47%)	71 (43%)	50 (31%)	379 (50%)	123 (49%)	148 (48%)	116 (38%)
Other	ANY	18 (29%)	28 (35%)	17 (10%)	22 (13%)	176 (23%)	58 (23%)	55 (18%)	72 (23%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	44 (71%)	53 (65%)	148 (90%)	141 (87%)	585 (77%)	192 (77%)	254 (82%)	235 (77%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINOVW_MENVSCONTROL_11_18SX

Table 82

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=89)	P6 Menomune (N=128)	P11 ACWY (N=192)	P11 Tdap (N=190)	P13 ACWY (N=867)	P13 Menactra (N=289)	P18 ACWY (N=232)	P18 Tdap (N=232)
Any	ANY	74 (83%)	91 (71%)	105 (55%)	153 (81%)	507 (58%)	187 (65%)	150 (65%)	175 (75%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	15 (17%)	37 (29%)	87 (45%)	37 (19%)	357 (41%)	102 (35%)	82 (35%)	57 (25%)
Local	ANY	61 (69%)	68 (53%)	69 (36%)	134 (71%)	385 (44%)	154 (53%)	109 (47%)	154 (66%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	28 (31%)	60 (47%)	123 (64%)	56 (29%)	479 (55%)	135 (47%)	123 (53%)	78 (34%)
Systemic	ANY	47 (53%)	59 (46%)	77 (40%)	89 (47%)	328 (38%)	107 (37%)	113 (49%)	118 (51%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	42 (47%)	69 (54%)	115 (60%)	101 (53%)	536 (62%)	182 (63%)	119 (51%)	114 (49%)
Other	ANY	22 (25%)	31 (24%)	16 (8%)	17 (9%)	136 (16%)	50 (17%)	42 (18%)	40 (17%)
	MISSING	0	0	0	0	3 (<1%)	0	0	0
	NONE	67 (75%)	97 (76%)	176 (92%)	173 (91%)	728 (84%)	239 (83%)	190 (82%)	192 (83%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINOVW_MENVSCONTROL_11_18SX

Table 83

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=62)	P11 ACWY (N=165)	P11 ACWY+Tdap (N=187)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 ACWY+HPV+Tdap (N=308)
Any	ANY	53 (85%)	116 (70%)	132 (71%)	537 (70%)	223 (72%)	245 (80%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	9 (15%)	49 (30%)	55 (29%)	224 (29%)	86 (28%)	63 (20%)
Local	ANY	46 (74%)	84 (51%)	55 (29%)	424 (55%)	170 (55%)	178 (58%)
	MISSING	0	0	0	4 (1%)	0	0
	NONE	16 (26%)	81 (49%)	132 (71%)	336 (44%)	139 (45%)	130 (42%)
Systemic	ANY	38 (61%)	94 (57%)	114 (61%)	382 (50%)	161 (52%)	196 (64%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	24 (39%)	71 (43%)	73 (39%)	379 (50%)	148 (48%)	112 (36%)
Other	ANY	18 (29%)	17 (10%)	24 (13%)	176 (23%)	55 (18%)	88 (29%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	44 (71%)	148 (90%)	163 (87%)	585 (77%)	254 (82%)	220 (71%)

Table 83

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=89)	P11 ACWY (N=192)	P11 ACWY+Tdap (N=172)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 ACWY+HPV+Tdap (N=232)
Any	ANY	74 (83%)	105 (55%)	104 (60%)	507 (58%)	150 (65%)	160 (69%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	15 (17%)	87 (45%)	68 (40%)	357 (41%)	82 (35%)	72 (31%)
Local	ANY	61 (69%)	69 (36%)	47 (27%)	385 (44%)	109 (47%)	111 (48%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	28 (31%)	123 (64%)	125 (73%)	479 (55%)	123 (53%)	121 (52%)
Systemic	ANY	47 (53%)	77 (40%)	84 (49%)	328 (38%)	113 (49%)	114 (49%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	42 (47%)	115 (60%)	88 (51%)	536 (62%)	119 (51%)	118 (51%)
Other	ANY	22 (25%)	16 (8%)	18 (10%)	136 (16%)	42 (18%)	45 (19%)
	MISSING	0	0	0	3 (<1%)	0	0
	NONE	67 (75%)	176 (92%)	154 (90%)	728 (84%)	190 (82%)	187 (81%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINOVW_MENVSCONVAC_11_18SX

Table 84

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=62)	P11 ACWY (N=165)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 Tdap, ACWY (N=293)
Any	ANY	53 (85%)	116 (70%)	537 (70%)	223 (72%)	212 (72%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	9 (15%)	49 (30%)	224 (29%)	86 (28%)	81 (28%)
Local	ANY	46 (74%)	84 (51%)	424 (55%)	170 (55%)	170 (58%)
	MISSING	0	0	4 (1%)	0	0
	NONE	16 (26%)	81 (49%)	336 (44%)	139 (45%)	123 (42%)
Systemic	ANY	38 (61%)	94 (57%)	382 (50%)	161 (52%)	146 (50%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	24 (39%)	71 (43%)	379 (50%)	148 (48%)	147 (50%)
Other	ANY	18 (29%)	17 (10%)	176 (23%)	55 (18%)	53 (18%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	44 (71%)	148 (90%)	585 (77%)	254 (82%)	240 (82%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINOVW_MENVSTDAP_11_18SX

Table 84

Summary of Subjects With At Least One Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: MALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=89)	P11 ACWY (N=192)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 Tdap, ACWY (N=210)
Any	ANY	74 (83%)	105 (55%)	507 (58%)	150 (65%)	110 (52%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	15 (17%)	87 (45%)	357 (41%)	82 (35%)	100 (48%)
Local	ANY	61 (69%)	69 (36%)	385 (44%)	109 (47%)	90 (43%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	28 (31%)	123 (64%)	479 (55%)	123 (53%)	120 (57%)
Systemic	ANY	47 (53%)	77 (40%)	328 (38%)	113 (49%)	69 (33%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	42 (47%)	115 (60%)	536 (62%)	119 (51%)	141 (67%)
Other	ANY	22 (25%)	16 (8%)	136 (16%)	42 (18%)	14 (7%)
	MISSING	0	0	3 (<1%)	0	0
	NONE	67 (75%)	176 (92%)	728 (84%)	190 (82%)	196 (93%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINOVW_MENVSTDAP_11_18SX

Table 85

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: FEMALE

	Ages 11-18 (N=1795)	Ages 19-34 (N=771)	Ages 35-55 (N=1079)	Total ACWY (N=3645)	Total Menactra (N=1113)
Any Reaction:					
NONE	508 (28%)	238 (31%)	437 (41%)	1183 (32%)	356 (32%)
OTHER THAN SEVERE	1106 (62%)	458 (59%)	558 (52%)	2122 (58%)	665 (60%)
SEVERE*	178 (10%)	75 (10%)	84 (8%)	337 (9%)	92 (8%)
MISSING	3 (<1%)	0	0	3 (<1%)	0
Local:					
NONE	834 (46%)	341 (44%)	587 (54%)	1762 (48%)	504 (45%)
MILD	887 (49%)	393 (51%)	443 (41%)	1723 (47%)	564 (51%)
SEVERE OR > 50MM*	70 (4%)	37 (5%)	49 (5%)	156 (4%)	45 (4%)
MISSING	4 (<1%)	0	0	4 (<1%)	0
Systemic:					
NONE	814 (45%)	421 (55%)	650 (60%)	1885 (52%)	612 (55%)
OTHER THAN SEVERE	840 (47%)	303 (39%)	377 (35%)	1520 (42%)	444 (40%)
SEVERE*	138 (8%)	47 (6%)	52 (5%)	237 (7%)	57 (5%)
MISSING	3 (<1%)	0	0	3 (<1%)	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.
*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_ACWY_SEX

Table 85

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: MALE

	Ages 11-18 (N=1784)	Ages 19-34 (N=374)	Ages 35-55 (N=382)	Total ACWY (N=2540)	Total Menactra (N=644)
Any Reaction:					
NONE	702 (39%)	172 (46%)	228 (60%)	1102 (43%)	274 (43%)
OTHER THAN SEVERE	937 (53%)	190 (51%)	138 (36%)	1265 (50%)	352 (55%)
SEVERE*	142 (8%)	12 (3%)	16 (4%)	170 (7%)	18 (3%)
MISSING	3 (<1%)	0	0	3 (<1%)	0
Local:					
NONE	999 (56%)	214 (57%)	269 (70%)	1482 (58%)	347 (54%)
MILD	720 (40%)	157 (42%)	109 (29%)	986 (39%)	288 (45%)
SEVERE OR > 50MM*	62 (3%)	3 (<1%)	4 (1%)	69 (3%)	9 (1%)
MISSING	3 (<1%)	0	0	3 (<1%)	0
Systemic:					
NONE	1024 (57%)	273 (73%)	288 (75%)	1585 (62%)	436 (68%)
OTHER THAN SEVERE	662 (37%)	92 (25%)	80 (21%)	834 (33%)	195 (30%)
SEVERE*	95 (5%)	9 (2%)	14 (4%)	118 (5%)	13 (2%)
MISSING	3 (<1%)	0	0	3 (<1%)	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine.
*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_ACWY_SEX

Table 86

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: FEMALE

	P6 ACWY (N=62)	P6 Menomune (N=81)	P11 ACWY (N=165)	P11 Tdap (N=163)	P13 ACWY (N=764)	P13 Menactra (N=250)	P18 ACWY (N=309)	P18 Tdap (N=307)
Any Reaction:								
NONE	10 (16%)	12 (15%)	50 (30%)	14 (9%)	232 (30%)	60 (24%)	88 (28%)	40 (13%)
OTHER THAN SEVERE	49 (79%)	65 (80%)	90 (55%)	122 (75%)	478 (63%)	172 (69%)	189 (61%)	229 (75%)
SEVERE*	3 (5%)	4 (5%)	25 (15%)	27 (17%)	51 (7%)	18 (7%)	32 (10%)	38 (12%)
MISSING	0	0	0	0	3 (<1%)	0	0	0
Local:								
NONE	16 (26%)	23 (28%)	81 (49%)	33 (20%)	336 (44%)	91 (36%)	139 (45%)	62 (20%)
MILD	45 (73%)	56 (69%)	74 (45%)	115 (71%)	396 (52%)	150 (60%)	162 (52%)	220 (72%)
SEVERE OR > 50MM*	1 (2%)	2 (2%)	10 (6%)	15 (9%)	28 (4%)	9 (4%)	8 (3%)	25 (8%)
MISSING	0	0	0	0	4 (<1%)	0	0	0
Systemic:								
NONE	24 (39%)	38 (47%)	71 (43%)	50 (31%)	385 (50%)	125 (50%)	148 (48%)	116 (38%)
OTHER THAN SEVERE	36 (58%)	41 (51%)	76 (46%)	98 (60%)	343 (45%)	116 (46%)	134 (43%)	167 (54%)
SEVERE*	2 (3%)	2 (2%)	18 (11%)	15 (9%)	33 (4%)	9 (4%)	27 (9%)	24 (8%)
MISSING	0	0	0	0	3 (<1%)	0	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSCONT_11_18SX.SAS(WARTERO) 11JUL08, 01:01 SAS.9.1- PINOVW_SEV_MENVSCONT_11_18SX

Table 86

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: MALE

	P6 ACWY (N=89)	P6 Menomune (N=128)	P11 ACWY (N=192)	P11 Tdap (N=190)	P13 ACWY (N=867)	P13 Menactra (N=289)	P18 ACWY (N=232)	P18 Tdap (N=232)
Any Reaction:								
NONE	15 (17%)	39 (30%)	87 (45%)	37 (19%)	373 (43%)	109 (38%)	86 (37%)	59 (25%)
OTHER THAN SEVERE	63 (71%)	84 (66%)	94 (49%)	139 (73%)	427 (49%)	172 (60%)	128 (55%)	152 (66%)
SEVERE*	11 (12%)	5 (4%)	11 (6%)	14 (7%)	64 (7%)	8 (3%)	18 (8%)	21 (9%)
MISSING	0	0	0	0	3 (<1%)	0	0	0
Local:								
NONE	28 (31%)	60 (47%)	123 (64%)	56 (29%)	479 (55%)	135 (47%)	123 (53%)	78 (34%)
MILD	55 (62%)	67 (52%)	65 (34%)	126 (66%)	351 (40%)	149 (52%)	100 (43%)	141 (61%)
SEVERE OR > 50MM*	6 (7%)	1 (<1%)	4 (2%)	8 (4%)	34 (4%)	5 (2%)	9 (4%)	13 (6%)
MISSING	0	0	0	0	3 (<1%)	0	0	0
Systemic:								
NONE	42 (47%)	69 (54%)	115 (60%)	101 (53%)	541 (62%)	188 (65%)	120 (52%)	117 (50%)
OTHER THAN SEVERE	40 (45%)	55 (43%)	67 (35%)	81 (43%)	289 (33%)	97 (34%)	101 (44%)	102 (44%)
SEVERE*	7 (8%)	4 (3%)	10 (5%)	8 (4%)	34 (4%)	4 (1%)	11 (5%)	13 (6%)
MISSING	0	0	0	0	3 (<1%)	0	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSCONT_11_18SX.SAS(WARTERO) 11JUL08, 01:01 SAS.9.1- PINOVW_SEV_MENVSCONT_11_18SX

Table 87

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: FEMALE

	P6 ACWY (N=62)	P11 ACWY (N=165)	P11 ACWY+Tdap (N=187)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 ACWY+HPV+Tdap (N=308)
Any Reaction:						
NONE	10 (16%)	50 (30%)	57 (30%)	232 (30%)	88 (28%)	71 (23%)
OTHER THAN SEVERE	49 (79%)	90 (55%)	111 (59%)	478 (63%)	189 (61%)	189 (61%)
SEVERE*	3 (5%)	25 (15%)	19 (10%)	51 (7%)	32 (10%)	48 (16%)
MISSING	0	0	0	3 (<1%)	0	0
Local:						
NONE	16 (26%)	81 (49%)	132 (71%)	336 (44%)	139 (45%)	130 (42%)
MILD	45 (73%)	74 (45%)	52 (28%)	396 (52%)	162 (52%)	158 (51%)
SEVERE OR > 50MM*	1 (2%)	10 (6%)	3 (2%)	28 (4%)	8 (3%)	20 (6%)
MISSING	0	0	0	4 (<1%)	0	0
Systemic:						
NONE	24 (39%)	71 (43%)	73 (39%)	385 (50%)	148 (48%)	113 (37%)
OTHER THAN SEVERE	36 (58%)	76 (46%)	95 (51%)	343 (45%)	134 (43%)	156 (51%)
SEVERE*	2 (3%)	18 (11%)	19 (10%)	33 (4%)	27 (9%)	39 (13%)
MISSING	0	0	0	3 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MENVSCONVAC_11_18SX

Table 87

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: MALE

	P6 ACWY (N=89)	P11 ACWY (N=192)	P11 ACWY+Tdap (N=172)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 ACWY+HPV+Tdap (N=232)
Any Reaction:						
NONE	15 (17%)	87 (45%)	68 (40%)	373 (43%)	86 (37%)	73 (31%)
OTHER THAN SEVERE	63 (71%)	94 (49%)	81 (47%)	427 (49%)	128 (55%)	144 (62%)
SEVERE*	11 (12%)	11 (6%)	23 (13%)	64 (7%)	18 (8%)	15 (6%)
MISSING	0	0	0	3 (<1%)	0	0
Local:						
NONE	28 (31%)	123 (64%)	125 (73%)	479 (55%)	123 (53%)	121 (52%)
MILD	55 (62%)	65 (34%)	44 (26%)	351 (40%)	100 (43%)	105 (45%)
SEVERE OR > 50MM*	6 (7%)	4 (2%)	3 (2%)	34 (4%)	9 (4%)	6 (3%)
MISSING	0	0	0	3 (<1%)	0	0
Systemic:						
NONE	42 (47%)	115 (60%)	88 (51%)	541 (62%)	120 (52%)	118 (51%)
OTHER THAN SEVERE	40 (45%)	67 (35%)	62 (36%)	289 (33%)	101 (44%)	103 (44%)
SEVERE*	7 (8%)	10 (5%)	22 (13%)	34 (4%)	11 (5%)	11 (5%)
MISSING	0	0	0	3 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MENVSCONVAC_11_18SX

Table 88

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: FEMALE

	P6 ACWY (N=62)	P11 ACWY (N=165)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 Tdap, ACWY (N=293)
Any Reaction:					
NONE	10 (16%)	50 (30%)	232 (30%)	88 (28%)	85 (29%)
OTHER THAN SEVERE	49 (79%)	90 (55%)	478 (63%)	189 (61%)	181 (62%)
SEVERE*	3 (5%)	25 (15%)	51 (7%)	32 (10%)	27 (9%)
MISSING	0	0	3 (<1%)	0	0
Local:					
NONE	16 (26%)	81 (49%)	336 (44%)	139 (45%)	123 (42%)
MILD	45 (73%)	74 (45%)	396 (52%)	162 (52%)	158 (54%)
SEVERE OR > 50MM*	1 (2%)	10 (6%)	28 (4%)	8 (3%)	12 (4%)
MISSING	0	0	4 (<1%)	0	0
Systemic:					
NONE	24 (39%)	71 (43%)	385 (50%)	148 (48%)	147 (50%)
OTHER THAN SEVERE	36 (58%)	76 (46%)	343 (45%)	134 (43%)	124 (42%)
SEVERE*	2 (3%)	18 (11%)	33 (4%)	27 (9%)	22 (8%)
MISSING	0	0	3 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MENVSTDAP_11_18SX

Table 88

Summary of Subjects With At Least One Severe Local and/or Systemic Reaction, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: MALE

	P6 ACWY (N=89)	P11 ACWY (N=192)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 Tdap, ACWY (N=210)
Any Reaction:					
NONE	15 (17%)	87 (45%)	373 (43%)	86 (37%)	102 (49%)
OTHER THAN SEVERE	63 (71%)	94 (49%)	427 (49%)	128 (55%)	94 (45%)
SEVERE*	11 (12%)	11 (6%)	64 (7%)	18 (8%)	14 (7%)
MISSING	0	0	3 (<1%)	0	0
Local:					
NONE	28 (31%)	123 (64%)	479 (55%)	123 (53%)	120 (57%)
MILD	55 (62%)	65 (34%)	351 (40%)	100 (43%)	83 (40%)
SEVERE OR > 50MM*	6 (7%)	4 (2%)	34 (4%)	9 (4%)	7 (3%)
MISSING	0	0	3 (<1%)	0	0
Systemic:					
NONE	42 (47%)	115 (60%)	541 (62%)	120 (52%)	142 (68%)
OTHER THAN SEVERE	40 (45%)	67 (35%)	289 (33%)	101 (44%)	57 (27%)
SEVERE*	7 (8%)	10 (5%)	34 (4%)	11 (5%)	11 (5%)
MISSING	0	0	3 (<1%)	0	0

*Severe pain or erythema/induration > 50mm. Severe fever is defined as temperature >= 39.0C.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\PINOVW_SEV_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:38 SAS.9.1- PINOVW_SEV_MENVSTDAP_11_18SX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: FEMALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1795)	Ages 19-34 (N=771)	Ages 35-55 (N=1079)	Total ACWY (N=3645)	Total Menactra (N=1113)
INJECTION SITE						
Pain	N	1791	771	1079	3641	1113
	ANY	861 (48%)	388 (50%)	423 (39%)	1672 (46%)	554 (50%)
	MILD	593 (33%)	281 (36%)	304 (28%)	1178 (32%)	397 (36%)
	MODERATE	234 (13%)	90 (12%)	95 (9%)	419 (12%)	126 (11%)
	SEVERE	34 (2%)	17 (2%)	24 (2%)	75 (2%)	31 (3%)
Erythema (mm)	N	1791	771	1079	3641	1113
	ANY	278 (16%)	135 (18%)	145 (13%)	558 (15%)	142 (13%)
	>0 - 25 mm	229 (13%)	99 (13%)	106 (10%)	434 (12%)	114 (10%)
	>25 - 50 mm	25 (1%)	16 (2%)	17 (2%)	58 (2%)	15 (1%)
	> 50 mm	24 (1%)	20 (3%)	22 (2%)	66 (2%)	13 (1%)
Induration (mm)	N	1791	771	1079	3641	1113
	ANY	251 (14%)	113 (15%)	133 (12%)	497 (14%)	144 (13%)
	>0 - 25 mm	179 (10%)	85 (11%)	103 (10%)	367 (10%)	113 (10%)
	>25 - 50 mm	40 (2%)	15 (2%)	17 (2%)	72 (2%)	18 (2%)
	> 50 mm	32 (2%)	13 (2%)	13 (1%)	58 (2%)	13 (1%)
SYSTEMIC						
Chills	N	1792	771	1079	3642	1113
	ANY	240 (13%)	68 (9%)	70 (6%)	378 (10%)	93 (8%)
	MILD	157 (9%)	45 (6%)	44 (4%)	246 (7%)	66 (6%)
	MODERATE	60 (3%)	15 (2%)	19 (2%)	94 (3%)	23 (2%)
	SEVERE	23 (1%)	8 (1%)	7 (1%)	38 (1%)	4 (<1%)
Nausea	N	1792	771	1079	3642	1113
	ANY	269 (15%)	81 (11%)	71 (7%)	421 (12%)	106 (10%)
	MILD	179 (10%)	59 (8%)	52 (5%)	290 (8%)	76 (7%)
	MODERATE	69 (4%)	16 (2%)	17 (2%)	102 (3%)	23 (2%)
	SEVERE	21 (1%)	6 (1%)	2 (<1%)	29 (1%)	7 (1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: FEMALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1795)	Ages 19-34 (N=771)	Ages 35-55 (N=1079)	Total ACWY (N=3645)	Total Menactra (N=1113)
SYSTEMIC						
Malaise	N	1792	771	1079	3642	1113
	ANY	317 (18%)	151 (20%)	164 (15%)	632 (17%)	204 (18%)
	MILD	180 (10%)	99 (13%)	97 (9%)	376 (10%)	124 (11%)
	MODERATE	105 (6%)	30 (4%)	49 (5%)	184 (5%)	62 (6%)
	SEVERE	32 (2%)	22 (3%)	18 (2%)	72 (2%)	18 (2%)
Myalgia	N	1792	771	1079	3642	1113
	ANY	451 (25%)	123 (16%)	142 (13%)	716 (20%)	200 (18%)
	MILD	298 (17%)	82 (11%)	86 (8%)	466 (13%)	121 (11%)
	MODERATE	106 (6%)	29 (4%)	44 (4%)	179 (5%)	65 (6%)
	SEVERE	47 (3%)	12 (2%)	12 (1%)	71 (2%)	14 (1%)
Arthralgia	N	1792	771	1079	3642	1113
	ANY	238 (13%)	59 (8%)	82 (8%)	379 (10%)	94 (8%)
	MILD	151 (8%)	43 (6%)	48 (4%)	242 (7%)	58 (5%)
	MODERATE	62 (3%)	12 (2%)	22 (2%)	96 (3%)	28 (3%)
	SEVERE	25 (1%)	4 (1%)	12 (1%)	41 (1%)	8 (1%)
Headache	N	1792	771	1079	3642	1113
	ANY	713 (40%)	251 (33%)	299 (28%)	1263 (35%)	363 (33%)
	MILD	422 (24%)	159 (21%)	194 (18%)	775 (21%)	234 (21%)
	MODERATE	202 (11%)	68 (9%)	72 (7%)	342 (9%)	100 (9%)
	SEVERE	89 (5%)	24 (3%)	33 (3%)	146 (4%)	29 (3%)
Rash	N	1378	771	1079	3228	1113
	ANY	56 (4%)	33 (4%)	33 (3%)	122 (4%)	28 (3%)
	OTHER	15 (1%)	10 (1%)	7 (1%)	32 (1%)	8 (1%)
	URTICARIAL	41 (3%)	23 (3%)	26 (2%)	90 (3%)	20 (2%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: FEMALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1795)	Ages 19-34 (N=771)	Ages 35-55 (N=1079)	Total ACWY (N=3645)	Total Menactra (N=1113)
SYSTEMIC						
Fever (>= 38C)	N	1788	771	1078	3637	1113
	YES	42 (2%)	24 (3%)	25 (2%)	91 (3%)	27 (2%)
	NO	1746 (98%)	747 (97%)	1053 (98%)	3546 (97%)	1086 (98%)
OTHER						
Stayed Home	N	1748	763	1077	3588	1107
	YES	97 (6%)	37 (5%)	35 (3%)	169 (5%)	45 (4%)
	NO	1651 (94%)	726 (95%)	1042 (97%)	3419 (95%)	1062 (96%)
Analgesic Antipyretics	N	1792	771	1079	3642	1112
	YES	332 (19%)	166 (22%)	237 (22%)	735 (20%)	242 (22%)
	NO	1460 (81%)	605 (78%)	842 (78%)	2907 (80%)	870 (78%)
Temperature (C)	N	1788	771	1078	3637	1113
	<38 C	1746 (98%)	747 (97%)	1053 (98%)	3546 (97%)	1086 (98%)
	38 - 38.9 C	35 (2%)	15 (2%)	20 (2%)	70 (2%)	18 (2%)
	39.0 - 39.9 C	5 (<1%)	7 (1%)	3 (<1%)	15 (<1%)	7 (1%)
	>= 40 C	2 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: MALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1784)	Ages 19-34 (N=374)	Ages 35-55 (N=382)	Total ACWY (N=2540)	Total Menactra (N=644)
INJECTION SITE						
Pain	N	1780	374	382	2536	644
	ANY	640 (36%)	122 (33%)	90 (24%)	852 (34%)	262 (41%)
	MILD	491 (28%)	99 (26%)	70 (18%)	660 (26%)	206 (32%)
	MODERATE	127 (7%)	21 (6%)	19 (5%)	167 (7%)	51 (8%)
	SEVERE	22 (1%)	2 (1%)	1 (<1%)	25 (1%)	5 (1%)
Erythema (mm)	N	1781	374	382	2537	644
	ANY	274 (15%)	57 (15%)	37 (10%)	368 (15%)	89 (14%)
	>0 - 25 mm	217 (12%)	57 (15%)	32 (8%)	306 (12%)	79 (12%)
	>25 - 50 mm	29 (2%)	0	2 (1%)	31 (1%)	6 (1%)
	> 50 mm	28 (2%)	0	3 (1%)	31 (1%)	4 (1%)
Induration (mm)	N	1781	374	382	2537	644
	ANY	217 (12%)	37 (10%)	24 (6%)	278 (11%)	59 (9%)
	>0 - 25 mm	160 (9%)	35 (9%)	23 (6%)	218 (9%)	50 (8%)
	>25 - 50 mm	30 (2%)	1 (<1%)	1 (<1%)	32 (1%)	7 (1%)
	> 50 mm	27 (2%)	1 (<1%)	0	28 (1%)	2 (<1%)
SYSTEMIC						
Chills	N	1781	374	382	2537	644
	ANY	140 (8%)	11 (3%)	16 (4%)	167 (7%)	27 (4%)
	MILD	95 (5%)	6 (2%)	8 (2%)	109 (4%)	18 (3%)
	MODERATE	35 (2%)	2 (1%)	6 (2%)	43 (2%)	7 (1%)
	SEVERE	10 (1%)	3 (1%)	2 (1%)	15 (1%)	2 (<1%)
Nausea	N	1781	374	382	2537	644
	ANY	171 (10%)	16 (4%)	17 (4%)	204 (8%)	36 (6%)
	MILD	114 (6%)	10 (3%)	12 (3%)	136 (5%)	21 (3%)
	MODERATE	45 (3%)	4 (1%)	1 (<1%)	50 (2%)	13 (2%)
	SEVERE	12 (1%)	2 (1%)	4 (1%)	18 (1%)	2 (<1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: MALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1784)	Ages 19-34 (N=374)	Ages 35-55 (N=382)	Total ACWY (N=2540)	Total Menactra (N=644)
SYSTEMIC						
Malaise	N	1781	374	382	2537	644
	ANY	233 (13%)	54 (14%)	42 (11%)	329 (13%)	81 (13%)
	MILD	146 (8%)	32 (9%)	22 (6%)	200 (8%)	51 (8%)
	MODERATE	64 (4%)	14 (4%)	16 (4%)	94 (4%)	26 (4%)
	SEVERE	23 (1%)	8 (2%)	4 (1%)	35 (1%)	4 (1%)
Myalgia	N	1781	374	382	2537	644
	ANY	340 (19%)	37 (10%)	37 (10%)	414 (16%)	80 (12%)
	MILD	221 (12%)	24 (6%)	22 (6%)	267 (11%)	59 (9%)
	MODERATE	92 (5%)	9 (2%)	13 (3%)	114 (4%)	18 (3%)
	SEVERE	27 (2%)	4 (1%)	2 (1%)	33 (1%)	3 (<1%)
Arthralgia	N	1781	374	382	2537	644
	ANY	164 (9%)	15 (4%)	22 (6%)	201 (8%)	36 (6%)
	MILD	115 (6%)	9 (2%)	15 (4%)	139 (5%)	26 (4%)
	MODERATE	33 (2%)	4 (1%)	5 (1%)	42 (2%)	8 (1%)
	SEVERE	16 (1%)	2 (1%)	2 (1%)	20 (1%)	2 (<1%)
Headache	N	1781	374	382	2537	644
	ANY	494 (28%)	65 (17%)	59 (15%)	618 (24%)	128 (20%)
	MILD	326 (18%)	44 (12%)	37 (10%)	407 (16%)	86 (13%)
	MODERATE	119 (7%)	18 (5%)	17 (4%)	154 (6%)	33 (5%)
	SEVERE	49 (3%)	3 (1%)	5 (1%)	57 (2%)	9 (1%)
Rash	N	1328	374	382	2084	644
	ANY	26 (2%)	6 (2%)	6 (2%)	38 (2%)	14 (2%)
	OTHER	7 (1%)	1 (<1%)	3 (1%)	11 (1%)	7 (1%)
	URTICARIAL	19 (1%)	5 (1%)	3 (1%)	27 (1%)	7 (1%)

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTER0) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 89

Summary of Reactogenicity on Days 1 to 7, Comparing Total MenACWY[1] across Age Groups and Gender

Gender: MALE

Reaction		Number (%) of Subjects Ages 11-18 (N=1784)	Ages 19-34 (N=374)	Ages 35-55 (N=382)	Total ACWY (N=2540)	Total Menactra (N=644)
SYSTEMIC						
Fever (>= 38C)	N	1776	374	380	2530	641
	YES	54 (3%)	7 (2%)	9 (2%)	70 (3%)	10 (2%)
	NO	1722 (97%)	367 (98%)	371 (98%)	2460 (97%)	631 (98%)
OTHER						
Stayed Home	N	1750	370	381	2501	638
	YES	79 (5%)	10 (3%)	10 (3%)	99 (4%)	18 (3%)
	NO	1671 (95%)	360 (97%)	371 (97%)	2402 (96%)	620 (97%)
Analgesic Antipyretics	N	1781	374	382	2537	644
	YES	244 (14%)	42 (11%)	45 (12%)	331 (13%)	84 (13%)
	NO	1537 (86%)	332 (89%)	337 (88%)	2206 (87%)	560 (87%)
Temperature (C)	N	1776	374	380	2530	641
	<38 C	1722 (97%)	367 (98%)	371 (98%)	2460 (97%)	631 (98%)
	38 - 38.9 C	42 (2%)	6 (2%)	7 (2%)	55 (2%)	9 (1%)
	39.0 - 39.9 C	12 (1%)	1 (<1%)	2 (1%)	15 (1%)	1 (<1%)
	>= 40 C	0	0	0	0	0

[1]All subjects who received either MenACWY alone or with a concomitant vaccine

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_ACWY_SEX.SAS(WARTERO) 10JUL08, 08:46 SAS.9.1 - PINJSUM_ACWY_SEX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=62)	P6 Menomune (N=81)	P11 ACWY (N=165)	P11 Tdap (N=163)	P13 ACWY (N=764)	P13 Menactra (N=250)	P18 ACWY (N=309)	P18 Tdap (N=307)
INJECTION SITE									
Pain	N	62	81	165	163	760	250	309	307
	ANY	34 (55%)	54 (67%)	68 (41%)	123 (75%)	391 (51%)	150 (60%)	156 (50%)	235 (77%)
	MILD	27 (44%)	43 (53%)	34 (21%)	55 (34%)	299 (39%)	114 (46%)	100 (32%)	130 (42%)
	MODERATE	7 (11%)	10 (12%)	27 (16%)	56 (34%)	84 (11%)	31 (12%)	52 (17%)	85 (28%)
	SEVERE	0	1 (1%)	7 (4%)	12 (7%)	8 (1%)	5 (2%)	4 (1%)	20 (7%)
Erythema (mm)	N	62	81	165	163	760	250	309	307
	ANY	27 (44%)	15 (19%)	37 (22%)	56 (34%)	114 (15%)	36 (14%)	40 (13%)	44 (14%)
	>0 - 25 mm	24 (39%)	14 (17%)	33 (20%)	50 (31%)	86 (11%)	30 (12%)	36 (12%)	41 (13%)
	>25 - 50 mm	3 (5%)	1 (1%)	3 (2%)	5 (3%)	13 (2%)	2 (1%)	2 (1%)	2 (1%)
	> 50 mm	0	0	1 (1%)	1 (1%)	15 (2%)	4 (2%)	2 (1%)	1 (<1%)
Induration (mm)	N	62	81	165	163	760	250	309	307
	ANY	17 (27%)	12 (15%)	35 (21%)	58 (36%)	92 (12%)	34 (14%)	37 (12%)	71 (23%)
	>0 - 25 mm	12 (19%)	11 (14%)	27 (16%)	43 (26%)	59 (8%)	27 (11%)	30 (10%)	53 (17%)
	>25 - 50 mm	4 (6%)	0	5 (3%)	13 (8%)	16 (2%)	4 (2%)	5 (2%)	14 (5%)
	> 50 mm	1 (2%)	1 (1%)	3 (2%)	2 (1%)	17 (2%)	3 (1%)	2 (1%)	4 (1%)
SYSTEMIC									
Chills	N	62	81	165	163	761	250	309	307
	ANY	13 (21%)	10 (12%)	32 (19%)	28 (17%)	74 (10%)	25 (10%)	43 (14%)	48 (16%)
	MILD	11 (18%)	7 (9%)	18 (11%)	19 (12%)	53 (7%)	19 (8%)	24 (8%)	36 (12%)
	MODERATE	1 (2%)	2 (2%)	10 (6%)	6 (4%)	15 (2%)	5 (2%)	14 (5%)	11 (4%)
	SEVERE	1 (2%)	1 (1%)	4 (2%)	3 (2%)	6 (1%)	1 (<1%)	5 (2%)	1 (<1%)
Nausea	N	62	81	165	163	761	250	309	307
	ANY	12 (19%)	7 (9%)	21 (13%)	26 (16%)	106 (14%)	26 (10%)	43 (14%)	56 (18%)
	MILD	9 (15%)	4 (5%)	15 (9%)	18 (11%)	69 (9%)	18 (7%)	24 (8%)	36 (12%)
	MODERATE	2 (3%)	2 (2%)	6 (4%)	6 (4%)	29 (4%)	6 (2%)	15 (5%)	18 (6%)
	SEVERE	1 (2%)	1 (1%)	0	2 (1%)	8 (1%)	2 (1%)	4 (1%)	2 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=62)	P6 Menomune (N=81)	P11 ACWY (N=165)	P11 Tdap (N=163)	P13 ACWY (N=764)	P13 Menactra (N=250)	P18 ACWY (N=309)	P18 Tdap (N=307)
SYSTEMIC									
Malaise	N	62	81	165	163	761	250	309	307
	ANY	10 (16%)	10 (12%)	23 (14%)	32 (20%)	96 (13%)	35 (14%)	67 (22%)	77 (25%)
	MILD	5 (8%)	5 (6%)	12 (7%)	21 (13%)	54 (7%)	20 (8%)	40 (13%)	46 (15%)
	MODERATE	3 (5%)	4 (5%)	8 (5%)	8 (5%)	37 (5%)	12 (5%)	21 (7%)	27 (9%)
	SEVERE	2 (3%)	1 (1%)	3 (2%)	3 (2%)	5 (1%)	3 (1%)	6 (2%)	4 (1%)
Myalgia	N	62	81	165	163	761	250	309	307
	ANY	20 (32%)	15 (19%)	42 (25%)	69 (42%)	163 (21%)	58 (23%)	67 (22%)	84 (27%)
	MILD	17 (27%)	8 (10%)	21 (13%)	43 (26%)	123 (16%)	39 (16%)	43 (14%)	55 (18%)
	MODERATE	3 (5%)	7 (9%)	14 (8%)	21 (13%)	27 (4%)	18 (7%)	19 (6%)	23 (7%)
	SEVERE	0	0	7 (4%)	5 (3%)	13 (2%)	1 (<1%)	5 (2%)	6 (2%)
Arthralgia	N	62	81	165	163	761	250	309	307
	ANY	6 (10%)	4 (5%)	25 (15%)	33 (20%)	68 (9%)	17 (7%)	42 (14%)	48 (16%)
	MILD	6 (10%)	2 (2%)	13 (8%)	21 (13%)	50 (7%)	14 (6%)	28 (9%)	31 (10%)
	MODERATE	0	2 (2%)	7 (4%)	11 (7%)	14 (2%)	3 (1%)	13 (4%)	13 (4%)
	SEVERE	0	0	5 (3%)	1 (1%)	4 (1%)	0	1 (<1%)	4 (1%)
Headache	N	62	81	165	163	761	250	309	307
	ANY	27 (44%)	35 (43%)	70 (42%)	69 (42%)	278 (37%)	91 (36%)	120 (39%)	134 (44%)
	MILD	20 (32%)	24 (30%)	42 (25%)	45 (28%)	181 (24%)	65 (26%)	60 (19%)	82 (27%)
	MODERATE	7 (11%)	10 (12%)	17 (10%)	17 (10%)	78 (10%)	21 (8%)	41 (13%)	36 (12%)
	SEVERE	0	1 (1%)	11 (7%)	7 (4%)	19 (2%)	5 (2%)	19 (6%)	16 (5%)
Rash	N	0	0	0	0	761	250	309	307
	ANY	0	0	0	0	26 (3%)	8 (3%)	13 (4%)	10 (3%)
	OTHER	0	0	0	0	14 (2%)	2 (1%)	1 (<1%)	1 (<1%)
	URTICARIAL	0	0	0	0	12 (2%)	6 (2%)	12 (4%)	9 (3%)
Fever (>= 38C)	N	62	81	165	163	757	250	309	307
	YES	0	1 (1%)	6 (4%)	3 (2%)	9 (1%)	2 (1%)	7 (2%)	9 (3%)
	NO	62 (100%)	80 (99%)	159 (96%)	160 (98%)	748 (99%)	248 (99%)	302 (98%)	298 (97%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=62)	P6 Menomune (N=81)	P11 ACWY (N=165)	P11 Tdap (N=163)	P13 ACWY (N=764)	P13 Menactra (N=250)	P18 ACWY (N=309)	P18 Tdap (N=307)
OTHER									
Stayed Home	N	61	81	165	163	755	248	290	294
	YES	2 (3%)	1 (1%)	5 (3%)	6 (4%)	23 (3%)	5 (2%)	25 (9%)	23 (8%)
	NO	59 (97%)	80 (99%)	160 (97%)	157 (96%)	732 (97%)	243 (98%)	265 (91%)	271 (92%)
Analgesic Antipyretics	N	62	81	165	163	761	250	309	307
	YES	17 (27%)	28 (35%)	17 (10%)	21 (13%)	169 (22%)	58 (23%)	41 (13%)	60 (20%)
	NO	45 (73%)	53 (65%)	148 (90%)	142 (87%)	592 (78%)	192 (77%)	268 (87%)	247 (80%)
Temperature (C)	N	62	81	165	163	757	250	309	307
	<38 C	62 (100%)	80 (99%)	159 (96%)	160 (98%)	748 (99%)	248 (99%)	302 (98%)	298 (97%)
	38 - 38.9 C	0	1 (1%)	6 (4%)	3 (2%)	7 (1%)	2 (1%)	7 (2%)	5 (2%)
	39.0 - 39.9 C	0	0	0	0	2 (<1%)	0	0	4 (1%)
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: MALE

Reaction		P6 ACWY (N=89)	P6 Menomune (N=128)	P11 ACWY (N=192)	P11 Tdap (N=190)	P13 ACWY (N=867)	P13 Menactra (N=289)	P18 ACWY (N=232)	P18 Tdap (N=232)
		Number (%) of Subjects							
INJECTION SITE									
Pain	N	89	128	192	190	863	289	232	232
	ANY	47 (53%)	60 (47%)	48 (25%)	123 (65%)	323 (37%)	137 (47%)	89 (38%)	148 (64%)
	MILD	40 (45%)	45 (35%)	38 (20%)	79 (42%)	261 (30%)	105 (36%)	62 (27%)	84 (36%)
	MODERATE	7 (8%)	14 (11%)	7 (4%)	39 (21%)	54 (6%)	30 (10%)	23 (10%)	55 (24%)
	SEVERE	0	1 (1%)	3 (2%)	5 (3%)	8 (1%)	2 (1%)	4 (2%)	9 (4%)
Erythema (mm)	N	89	128	192	190	864	289	232	232
	ANY	30 (34%)	24 (19%)	29 (15%)	47 (25%)	133 (15%)	49 (17%)	26 (11%)	26 (11%)
	>0 - 25 mm	24 (27%)	24 (19%)	25 (13%)	37 (19%)	94 (11%)	40 (14%)	24 (10%)	24 (10%)
	>25 - 50 mm	1 (1%)	0	4 (2%)	8 (4%)	18 (2%)	6 (2%)	1 (<1%)	2 (1%)
	> 50 mm	5 (6%)	0	0	2 (1%)	21 (2%)	3 (1%)	1 (<1%)	0
Induration (mm)	N	89	128	192	190	864	289	232	232
	ANY	17 (19%)	11 (9%)	24 (13%)	60 (32%)	104 (12%)	25 (9%)	33 (14%)	38 (16%)
	>0 - 25 mm	12 (13%)	11 (9%)	18 (9%)	37 (19%)	76 (9%)	18 (6%)	26 (11%)	27 (12%)
	>25 - 50 mm	0	0	5 (3%)	19 (10%)	14 (2%)	6 (2%)	3 (1%)	6 (3%)
	> 50 mm	5 (6%)	0	1 (1%)	4 (2%)	14 (2%)	1 (<1%)	4 (2%)	5 (2%)
SYSTEMIC									
Chills	N	89	128	192	190	864	289	232	232
	ANY	11 (12%)	6 (5%)	15 (8%)	13 (7%)	53 (6%)	13 (4%)	23 (10%)	22 (9%)
	MILD	6 (7%)	5 (4%)	11 (6%)	12 (6%)	35 (4%)	10 (3%)	18 (8%)	15 (6%)
	MODERATE	4 (4%)	1 (1%)	2 (1%)	1 (1%)	15 (2%)	3 (1%)	4 (2%)	6 (3%)
	SEVERE	1 (1%)	0	2 (1%)	0	3 (<1%)	0	1 (<1%)	1 (<1%)
Nausea	N	89	128	192	190	864	289	232	232
	ANY	10 (11%)	13 (10%)	7 (4%)	9 (5%)	81 (9%)	21 (7%)	29 (13%)	26 (11%)
	MILD	6 (7%)	10 (8%)	2 (1%)	7 (4%)	53 (6%)	12 (4%)	21 (9%)	20 (9%)
	MODERATE	3 (3%)	2 (2%)	1 (1%)	2 (1%)	26 (3%)	7 (2%)	8 (3%)	6 (3%)
	SEVERE	1 (1%)	1 (1%)	4 (2%)	0	2 (<1%)	2 (1%)	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=89)	P6 Menomune (N=128)	P11 ACWY (N=192)	P11 Tdap (N=190)	P13 ACWY (N=867)	P13 Menactra (N=289)	P18 ACWY (N=232)	P18 Tdap (N=232)
SYSTEMIC									
Malaise	N	89	128	192	190	864	289	232	232
	ANY	13 (15%)	11 (9%)	20 (10%)	25 (13%)	81 (9%)	30 (10%)	43 (19%)	38 (16%)
	MILD	8 (9%)	8 (6%)	11 (6%)	19 (10%)	51 (6%)	14 (5%)	31 (13%)	20 (9%)
	MODERATE	4 (4%)	3 (2%)	7 (4%)	4 (2%)	19 (2%)	14 (5%)	11 (5%)	16 (7%)
	SEVERE	1 (1%)	0	2 (1%)	2 (1%)	11 (1%)	2 (1%)	1 (<1%)	2 (1%)
Myalgia	N	89	128	192	190	864	289	232	232
	ANY	15 (17%)	15 (12%)	37 (19%)	58 (31%)	147 (17%)	41 (14%)	37 (16%)	57 (25%)
	MILD	11 (12%)	11 (9%)	25 (13%)	38 (20%)	100 (12%)	29 (10%)	24 (10%)	33 (14%)
	MODERATE	3 (3%)	4 (3%)	10 (5%)	16 (8%)	36 (4%)	11 (4%)	11 (5%)	19 (8%)
	SEVERE	1 (1%)	0	2 (1%)	4 (2%)	11 (1%)	1 (<1%)	2 (1%)	5 (2%)
Arthralgia	N	89	128	192	190	864	289	232	232
	ANY	6 (7%)	3 (2%)	15 (8%)	27 (14%)	69 (8%)	17 (6%)	20 (9%)	28 (12%)
	MILD	6 (7%)	1 (1%)	11 (6%)	14 (7%)	52 (6%)	13 (4%)	12 (5%)	17 (7%)
	MODERATE	0	2 (2%)	0	10 (5%)	14 (2%)	4 (1%)	6 (3%)	9 (4%)
	SEVERE	0	0	4 (2%)	3 (2%)	3 (<1%)	0	2 (1%)	2 (1%)
Headache	N	89	128	192	190	864	289	232	232
	ANY	35 (39%)	47 (37%)	58 (30%)	41 (22%)	200 (23%)	62 (21%)	74 (32%)	66 (28%)
	MILD	22 (25%)	30 (23%)	40 (21%)	31 (16%)	141 (16%)	42 (15%)	41 (18%)	37 (16%)
	MODERATE	6 (7%)	13 (10%)	10 (5%)	6 (3%)	45 (5%)	18 (6%)	29 (13%)	21 (9%)
	SEVERE	7 (8%)	4 (3%)	8 (4%)	4 (2%)	14 (2%)	2 (1%)	4 (2%)	8 (3%)
Rash	N	0	0	0	0	864	289	232	232
	ANY	0	0	0	0	18 (2%)	10 (3%)	4 (2%)	10 (4%)
	OTHER	0	0	0	0	7 (1%)	6 (2%)	0	2 (1%)
	URTICARIAL	0	0	0	0	11 (1%)	4 (1%)	4 (2%)	8 (3%)
Fever (>= 38C)	N	89	128	192	190	859	286	232	232
	YES	1 (1%)	3 (2%)	8 (4%)	4 (2%)	14 (2%)	2 (1%)	12 (5%)	8 (3%)
	NO	88 (99%)	125 (98%)	184 (96%)	186 (98%)	845 (98%)	284 (99%)	220 (95%)	224 (97%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 90

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs. Controls by Study within Age Group and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects							
		P6 ACWY (N=89)	P6 Menomune (N=128)	P11 ACWY (N=192)	P11 Tdap (N=190)	P13 ACWY (N=867)	P13 Menactra (N=289)	P18 ACWY (N=232)	P18 Tdap (N=232)
OTHER									
Stayed Home	N	89	128	192	190	856	284	219	208
	YES	4 (4%)	3 (2%)	7 (4%)	9 (5%)	29 (3%)	9 (3%)	15 (7%)	16 (8%)
	NO	85 (96%)	125 (98%)	185 (96%)	181 (95%)	827 (97%)	275 (97%)	204 (93%)	192 (92%)
Analgesic Antipyretics	N	89	128	192	190	864	289	232	232
	YES	22 (25%)	31 (24%)	14 (7%)	17 (9%)	124 (14%)	46 (16%)	32 (14%)	32 (14%)
	NO	67 (75%)	97 (76%)	178 (93%)	173 (91%)	740 (86%)	243 (84%)	200 (86%)	200 (86%)
Temperature (C)	N	89	128	192	190	859	286	232	232
	<38 C	88 (99%)	125 (98%)	184 (96%)	186 (98%)	845 (98%)	284 (99%)	220 (95%)	224 (97%)
	38 - 38.9 C	1 (1%)	3 (2%)	5 (3%)	4 (2%)	10 (1%)	2 (1%)	8 (3%)	7 (3%)
	39.0 - 39.9 C	0	0	3 (2%)	0	4 (<1%)	0	4 (2%)	1 (<1%)
	>= 40 C	0	0	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONTROL_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONTROL_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=62)	P11 ACWY (N=165)	P11 ACWY+Tdap (N=187)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 ACWY+HPV+Tdap (N=308)
INJECTION SITE							
Pain	N	62	165	187	760	309	308
	ANY	34 (55%)	68 (41%)	46 (25%)	391 (51%)	156 (50%)	166 (54%)
	MILD	27 (44%)	34 (21%)	23 (12%)	299 (39%)	100 (32%)	110 (36%)
	MODERATE	7 (11%)	27 (16%)	20 (11%)	84 (11%)	52 (17%)	44 (14%)
	SEVERE	0	7 (4%)	3 (2%)	8 (1%)	4 (1%)	12 (4%)
Erythema (mm)	N	62	165	187	760	309	308
	ANY	27 (44%)	37 (22%)	18 (10%)	114 (15%)	40 (13%)	42 (14%)
	>0 - 25 mm	24 (39%)	33 (20%)	17 (9%)	86 (11%)	36 (12%)	33 (11%)
	>25 - 50 mm	3 (5%)	3 (2%)	1 (1%)	13 (2%)	2 (1%)	3 (1%)
	> 50 mm	0	1 (1%)	0	15 (2%)	2 (1%)	6 (2%)
Induration (mm)	N	62	165	187	760	309	308
	ANY	17 (27%)	35 (21%)	24 (13%)	92 (12%)	37 (12%)	46 (15%)
	>0 - 25 mm	12 (19%)	27 (16%)	19 (10%)	59 (8%)	30 (10%)	32 (10%)
	>25 - 50 mm	4 (6%)	5 (3%)	5 (3%)	16 (2%)	5 (2%)	5 (2%)
	> 50 mm	1 (2%)	3 (2%)	0	17 (2%)	2 (1%)	9 (3%)
SYSTEMIC							
Chills	N	62	165	187	761	309	308
	ANY	13 (21%)	32 (19%)	23 (12%)	74 (10%)	43 (14%)	55 (18%)
	MILD	11 (18%)	18 (11%)	17 (9%)	53 (7%)	24 (8%)	34 (11%)
	MODERATE	1 (2%)	10 (6%)	4 (2%)	15 (2%)	14 (5%)	16 (5%)
	SEVERE	1 (2%)	4 (2%)	2 (1%)	6 (1%)	5 (2%)	5 (2%)
Nausea	N	62	165	187	761	309	308
	ANY	12 (19%)	21 (13%)	23 (12%)	106 (14%)	43 (14%)	64 (21%)
	MILD	9 (15%)	15 (9%)	21 (11%)	69 (9%)	24 (8%)	41 (13%)
	MODERATE	2 (3%)	6 (4%)	1 (1%)	29 (4%)	15 (5%)	16 (5%)
	SEVERE	1 (2%)	0	1 (1%)	8 (1%)	4 (1%)	7 (2%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=62)	P11 ACWY (N=165)	P11 ACWY+Tdap (N=187)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 ACWY+HPV+Tdap (N=308)
SYSTEMIC							
Malaise	N	62	165	187	761	309	308
	ANY	10 (16%)	23 (14%)	40 (21%)	96 (13%)	67 (22%)	81 (26%)
	MILD	5 (8%)	12 (7%)	24 (13%)	54 (7%)	40 (13%)	45 (15%)
	MODERATE	3 (5%)	8 (5%)	12 (6%)	37 (5%)	21 (7%)	24 (8%)
	SEVERE	2 (3%)	3 (2%)	4 (2%)	5 (1%)	6 (2%)	12 (4%)
Myalgia	N	62	165	187	761	309	308
	ANY	20 (32%)	42 (25%)	67 (36%)	163 (21%)	67 (22%)	92 (30%)
	MILD	17 (27%)	21 (13%)	31 (17%)	123 (16%)	43 (14%)	63 (20%)
	MODERATE	3 (5%)	14 (8%)	28 (15%)	27 (4%)	19 (6%)	15 (5%)
	SEVERE	0	7 (4%)	8 (4%)	13 (2%)	5 (2%)	14 (5%)
Arthralgia	N	62	165	187	761	309	308
	ANY	6 (10%)	25 (15%)	32 (17%)	68 (9%)	42 (14%)	65 (21%)
	MILD	6 (10%)	13 (8%)	14 (7%)	50 (7%)	28 (9%)	40 (13%)
	MODERATE	0	7 (4%)	15 (8%)	14 (2%)	13 (4%)	13 (4%)
	SEVERE	0	5 (3%)	3 (2%)	4 (1%)	1 (<1%)	12 (4%)
Headache	N	62	165	187	761	309	308
	ANY	27 (44%)	70 (42%)	77 (41%)	278 (37%)	120 (39%)	141 (46%)
	MILD	20 (32%)	42 (25%)	42 (22%)	181 (24%)	60 (19%)	77 (25%)
	MODERATE	7 (11%)	17 (10%)	20 (11%)	78 (10%)	41 (13%)	39 (13%)
	SEVERE	0	11 (7%)	15 (8%)	19 (2%)	19 (6%)	25 (8%)
Rash	N	0	0	0	761	309	308
	ANY	0	0	0	26 (3%)	13 (4%)	17 (6%)
	OTHER	0	0	0	14 (2%)	1 (<1%)	0
	URTICARIAL	0	0	0	12 (2%)	12 (4%)	17 (6%)
Fever (>= 38C)	N	62	165	187	757	309	308
	YES	0	6 (4%)	4 (2%)	9 (1%)	7 (2%)	16 (5%)
	NO	62 (100%)	159 (96%)	183 (98%)	748 (99%)	302 (98%)	292 (95%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=62)	P11 ACWY (N=165)	P11 ACWY+Tdap (N=187)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 ACWY+HPV+Tdap (N=308)
OTHER							
Stayed Home	N	61	165	187	755	290	290
	YES	2 (3%)	5 (3%)	6 (3%)	23 (3%)	25 (9%)	36 (12%)
	NO	59 (97%)	160 (97%)	181 (97%)	732 (97%)	265 (91%)	254 (88%)
Analgesic Antipyretics	N	62	165	187	761	309	308
	YES	17 (27%)	17 (10%)	22 (12%)	169 (22%)	41 (13%)	66 (21%)
	NO	45 (73%)	148 (90%)	165 (88%)	592 (78%)	268 (87%)	242 (79%)
Temperature (C)	N	62	165	187	757	309	308
	<38 C	62 (100%)	159 (96%)	183 (98%)	748 (99%)	302 (98%)	292 (95%)
	38 - 38.9 C	0	6 (4%)	2 (1%)	7 (1%)	7 (2%)	13 (4%)
	39.0 - 39.9 C	0	0	2 (1%)	2 (<1%)	0	1 (<1%)
	>= 40 C	0	0	0	0	0	2 (1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=89)	P11 ACWY (N=192)	P11 ACWY+Tdap (N=172)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 ACWY+HPV+Tdap (N=232)
INJECTION SITE							
Pain	N	89	192	172	863	232	232
	ANY	47 (53%)	48 (25%)	36 (21%)	323 (37%)	89 (38%)	97 (42%)
	MILD	40 (45%)	38 (20%)	29 (17%)	261 (30%)	62 (27%)	61 (26%)
	MODERATE	7 (8%)	7 (4%)	4 (2%)	54 (6%)	23 (10%)	32 (14%)
	SEVERE	0	3 (2%)	3 (2%)	8 (1%)	4 (2%)	4 (2%)
Erythema (mm)	N	89	192	172	864	232	232
	ANY	30 (34%)	29 (15%)	30 (17%)	133 (15%)	26 (11%)	26 (11%)
	>0 - 25 mm	24 (27%)	25 (13%)	24 (14%)	94 (11%)	24 (10%)	26 (11%)
	>25 - 50 mm	1 (1%)	4 (2%)	5 (3%)	18 (2%)	1 (<1%)	0
	> 50 mm	5 (6%)	0	1 (1%)	21 (2%)	1 (<1%)	0
Induration (mm)	N	89	192	172	864	232	232
	ANY	17 (19%)	24 (13%)	17 (10%)	104 (12%)	33 (14%)	22 (9%)
	>0 - 25 mm	12 (13%)	18 (9%)	10 (6%)	76 (9%)	26 (11%)	18 (8%)
	>25 - 50 mm	0	5 (3%)	6 (3%)	14 (2%)	3 (1%)	2 (1%)
	> 50 mm	5 (6%)	1 (1%)	1 (1%)	14 (2%)	4 (2%)	2 (1%)
SYSTEMIC							
Chills	N	89	192	172	864	232	232
	ANY	11 (12%)	15 (8%)	16 (9%)	53 (6%)	23 (10%)	22 (9%)
	MILD	6 (7%)	11 (6%)	12 (7%)	35 (4%)	18 (8%)	13 (6%)
	MODERATE	4 (4%)	2 (1%)	3 (2%)	15 (2%)	4 (2%)	7 (3%)
	SEVERE	1 (1%)	2 (1%)	1 (1%)	3 (<1%)	1 (<1%)	2 (1%)
Nausea	N	89	192	172	864	232	232
	ANY	10 (11%)	7 (4%)	20 (12%)	81 (9%)	29 (13%)	24 (10%)
	MILD	6 (7%)	2 (1%)	12 (7%)	53 (6%)	21 (9%)	20 (9%)
	MODERATE	3 (3%)	1 (1%)	4 (2%)	26 (3%)	8 (3%)	3 (1%)
	SEVERE	1 (1%)	4 (2%)	4 (2%)	2 (<1%)	0	1 (<1%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects					
		P6 ACWY (N=89)	P11 ACWY (N=192)	P11 ACWY+Tdap (N=172)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 ACWY+HPV+Tdap (N=232)
SYSTEMIC							
Malaise	N	89	192	172	864	232	232
	ANY	13 (15%)	20 (10%)	25 (15%)	81 (9%)	43 (19%)	51 (22%)
	MILD	8 (9%)	11 (6%)	11 (6%)	51 (6%)	31 (13%)	34 (15%)
	MODERATE	4 (4%)	7 (4%)	9 (5%)	19 (2%)	11 (5%)	14 (6%)
	SEVERE	1 (1%)	2 (1%)	5 (3%)	11 (1%)	1 (<1%)	3 (1%)
Myalgia	N	89	192	172	864	232	232
	ANY	15 (17%)	37 (19%)	51 (30%)	147 (17%)	37 (16%)	53 (23%)
	MILD	11 (12%)	25 (13%)	27 (16%)	100 (12%)	24 (10%)	34 (15%)
	MODERATE	3 (3%)	10 (5%)	16 (9%)	36 (4%)	11 (5%)	16 (7%)
	SEVERE	1 (1%)	2 (1%)	8 (5%)	11 (1%)	2 (1%)	3 (1%)
Arthralgia	N	89	192	172	864	232	232
	ANY	6 (7%)	15 (8%)	25 (15%)	69 (8%)	20 (9%)	29 (13%)
	MILD	6 (7%)	11 (6%)	14 (8%)	52 (6%)	12 (5%)	20 (9%)
	MODERATE	0	0	4 (2%)	14 (2%)	6 (3%)	9 (4%)
	SEVERE	0	4 (2%)	7 (4%)	3 (<1%)	2 (1%)	0
Headache	N	89	192	172	864	232	232
	ANY	35 (39%)	58 (30%)	52 (30%)	200 (23%)	74 (32%)	75 (32%)
	MILD	22 (25%)	40 (21%)	28 (16%)	141 (16%)	41 (18%)	54 (23%)
	MODERATE	6 (7%)	10 (5%)	14 (8%)	45 (5%)	29 (13%)	15 (6%)
	SEVERE	7 (8%)	8 (4%)	10 (6%)	14 (2%)	4 (2%)	6 (3%)
Rash	N	0	0	0	864	232	232
	ANY	0	0	0	18 (2%)	4 (2%)	4 (2%)
	OTHER	0	0	0	7 (1%)	0	0
	URTICARIAL	0	0	0	11 (1%)	4 (2%)	4 (2%)
Fever (>= 38C)	N	89	192	172	859	232	232
	YES	1 (1%)	8 (4%)	7 (4%)	14 (2%)	12 (5%)	12 (5%)
	NO	88 (99%)	184 (96%)	165 (96%)	845 (98%)	220 (95%)	220 (95%)

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 91

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY+Concomitant Vaccines by Study and Gender
Ages 11-18

Gender: MALE

Reaction		Number (%) of Subjects P6 ACWY (N=89)	P11 ACWY (N=192)	P11 ACWY+Tdap (N=172)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 ACWY+HPV+Tdap (N=232)
OTHER							
Stayed Home	N	89	192	171	856	219	223
	YES	4 (4%)	7 (4%)	6 (4%)	29 (3%)	15 (7%)	18 (8%)
	NO	85 (96%)	185 (96%)	165 (96%)	827 (97%)	204 (93%)	205 (92%)
Analgesic Antipyretics	N	89	192	172	864	232	232
	YES	22 (25%)	14 (7%)	16 (9%)	124 (14%)	32 (14%)	36 (16%)
	NO	67 (75%)	178 (93%)	156 (91%)	740 (86%)	200 (86%)	196 (84%)
Temperature (C)	N	89	192	172	859	232	232
	<38 C	88 (99%)	184 (96%)	165 (96%)	845 (98%)	220 (95%)	220 (95%)
	38 - 38.9 C	1 (1%)	5 (3%)	7 (4%)	10 (1%)	8 (3%)	11 (5%)
	39.0 - 39.9 C	0	3 (2%)	0	4 (<1%)	4 (2%)	1 (<1%)
	>= 40 C	0	0	0	0	0	0

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSCONVAC_11_18SX.SAS(WARTERO) 10JUL08, 08:47 SAS.9.1 - PINJSUM_MENVSCONVAC_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=62)	P11 ACWY (N=165)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 Tdap, ACWY (N=293)
INJECTION SITE						
Pain	N	62	165	760	309	293
	ANY	34 (55%)	68 (41%)	391 (51%)	156 (50%)	156 (53%)
	MILD	27 (44%)	34 (21%)	299 (39%)	100 (32%)	99 (34%)
	MODERATE	7 (11%)	27 (16%)	84 (11%)	52 (17%)	47 (16%)
	SEVERE	0	7 (4%)	8 (1%)	4 (1%)	10 (3%)
Erythema (mm)	N	62	165	760	309	293
	ANY	27 (44%)	37 (22%)	114 (15%)	40 (13%)	41 (14%)
	>0 - 25 mm	24 (39%)	33 (20%)	86 (11%)	36 (12%)	38 (13%)
	>25 - 50 mm	3 (5%)	3 (2%)	13 (2%)	2 (1%)	0
	> 50 mm	0	1 (1%)	15 (2%)	2 (1%)	3 (1%)
Induration (mm)	N	62	165	760	309	293
	ANY	17 (27%)	35 (21%)	92 (12%)	37 (12%)	40 (14%)
	>0 - 25 mm	12 (19%)	27 (16%)	59 (8%)	30 (10%)	34 (12%)
	>25 - 50 mm	4 (6%)	5 (3%)	16 (2%)	5 (2%)	3 (1%)
	> 50 mm	1 (2%)	3 (2%)	17 (2%)	2 (1%)	3 (1%)
SYSTEMIC						
Chills	N	62	165	761	309	293
	ANY	13 (21%)	32 (19%)	74 (10%)	43 (14%)	29 (10%)
	MILD	11 (18%)	18 (11%)	53 (7%)	24 (8%)	22 (8%)
	MODERATE	1 (2%)	10 (6%)	15 (2%)	14 (5%)	3 (1%)
	SEVERE	1 (2%)	4 (2%)	6 (1%)	5 (2%)	4 (1%)
Nausea	N	62	165	761	309	293
	ANY	12 (19%)	21 (13%)	106 (14%)	43 (14%)	48 (16%)
	MILD	9 (15%)	15 (9%)	69 (9%)	24 (8%)	34 (12%)
	MODERATE	2 (3%)	6 (4%)	29 (4%)	15 (5%)	10 (3%)
	SEVERE	1 (2%)	0	8 (1%)	4 (1%)	4 (1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=62)	P11 ACWY (N=165)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 Tdap, ACWY (N=293)
SYSTEMIC						
Malaise	N	62	165	761	309	293
	ANY	10 (16%)	23 (14%)	96 (13%)	67 (22%)	59 (20%)
	MILD	5 (8%)	12 (7%)	54 (7%)	40 (13%)	34 (12%)
	MODERATE	3 (5%)	8 (5%)	37 (5%)	21 (7%)	14 (5%)
	SEVERE	2 (3%)	3 (2%)	5 (1%)	6 (2%)	11 (4%)
Myalgia	N	62	165	761	309	293
	ANY	20 (32%)	42 (25%)	163 (21%)	67 (22%)	53 (18%)
	MILD	17 (27%)	21 (13%)	123 (16%)	43 (14%)	34 (12%)
	MODERATE	3 (5%)	14 (8%)	27 (4%)	19 (6%)	14 (5%)
	SEVERE	0	7 (4%)	13 (2%)	5 (2%)	5 (2%)
Arthralgia	N	62	165	761	309	293
	ANY	6 (10%)	25 (15%)	68 (9%)	42 (14%)	35 (12%)
	MILD	6 (10%)	13 (8%)	50 (7%)	28 (9%)	22 (8%)
	MODERATE	0	7 (4%)	14 (2%)	13 (4%)	12 (4%)
	SEVERE	0	5 (3%)	4 (1%)	1 (<1%)	1 (<1%)
Headache	N	62	165	761	309	293
	ANY	27 (44%)	70 (42%)	278 (37%)	120 (39%)	94 (32%)
	MILD	20 (32%)	42 (25%)	181 (24%)	60 (19%)	48 (16%)
	MODERATE	7 (11%)	17 (10%)	78 (10%)	41 (13%)	35 (12%)
	SEVERE	0	11 (7%)	19 (2%)	19 (6%)	11 (4%)
Rash	N	0	0	761	309	293
	ANY	0	0	26 (3%)	13 (4%)	8 (3%)
	OTHER	0	0	14 (2%)	1 (<1%)	0
	URTICARIAL	0	0	12 (2%)	12 (4%)	8 (3%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: FEMALE

Reaction[1]		Number (%) of Subjects P6 ACWY (N=62)	P11 ACWY (N=165)	P13 ACWY (N=764)	P18 ACWY (N=309)	P18 Tdap, ACWY (N=293)
SYSTEMIC						
Fever (>= 38C)	N	62	165	757	309	293
	YES	0	6 (4%)	9 (1%)	7 (2%)	19 (6%)
	NO	62 (100%)	159 (96%)	748 (99%)	302 (98%)	274 (94%)
OTHER						
Stayed Home	N	61	165	755	290	286
	YES	2 (3%)	5 (3%)	23 (3%)	25 (9%)	18 (6%)
	NO	59 (97%)	160 (97%)	732 (97%)	265 (91%)	268 (94%)
Analgesic Antipyretics	N	62	165	761	309	293
	YES	17 (27%)	17 (10%)	169 (22%)	41 (13%)	40 (14%)
	NO	45 (73%)	148 (90%)	592 (78%)	268 (87%)	253 (86%)
Temperature (C)	N	62	165	757	309	293
	<38 C	62 (100%)	159 (96%)	748 (99%)	302 (98%)	274 (94%)
	38 - 38.9 C	0	6 (4%)	7 (1%)	7 (2%)	15 (5%)
	39.0 - 39.9 C	0	0	2 (<1%)	0	4 (1%)
	>= 40 C	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: MALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=89)	P11 ACWY (N=192)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 Tdap, ACWY (N=210)
INJECTION SITE						
Pain	N	89	192	863	232	210
	ANY	47 (53%)	48 (25%)	323 (37%)	89 (38%)	83 (40%)
	MILD	40 (45%)	38 (20%)	261 (30%)	62 (27%)	54 (26%)
	MODERATE	7 (8%)	7 (4%)	54 (6%)	23 (10%)	23 (11%)
	SEVERE	0	3 (2%)	8 (1%)	4 (2%)	6 (3%)
Erythema (mm)	N	89	192	864	232	210
	ANY	30 (34%)	29 (15%)	133 (15%)	26 (11%)	23 (11%)
	>0 - 25 mm	24 (27%)	25 (13%)	94 (11%)	24 (10%)	18 (9%)
	>25 - 50 mm	1 (1%)	4 (2%)	18 (2%)	1 (<1%)	2 (1%)
	> 50 mm	5 (6%)	0	21 (2%)	1 (<1%)	3 (1%)
Induration (mm)	N	89	192	864	232	210
	ANY	17 (19%)	24 (13%)	104 (12%)	33 (14%)	24 (11%)
	>0 - 25 mm	12 (13%)	18 (9%)	76 (9%)	26 (11%)	19 (9%)
	>25 - 50 mm	0	5 (3%)	14 (2%)	3 (1%)	3 (1%)
	> 50 mm	5 (6%)	1 (1%)	14 (2%)	4 (2%)	2 (1%)
SYSTEMIC						
Chills	N	89	192	864	232	210
	ANY	11 (12%)	15 (8%)	53 (6%)	23 (10%)	16 (8%)
	MILD	6 (7%)	11 (6%)	35 (4%)	18 (8%)	10 (5%)
	MODERATE	4 (4%)	2 (1%)	15 (2%)	4 (2%)	4 (2%)
	SEVERE	1 (1%)	2 (1%)	3 (<1%)	1 (<1%)	2 (1%)
Nausea	N	89	192	864	232	210
	ANY	10 (11%)	7 (4%)	81 (9%)	29 (13%)	16 (8%)
	MILD	6 (7%)	2 (1%)	53 (6%)	21 (9%)	13 (6%)
	MODERATE	3 (3%)	1 (1%)	26 (3%)	8 (3%)	2 (1%)
	SEVERE	1 (1%)	4 (2%)	2 (<1%)	0	1 (<1%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: MALE

Reaction[1]		Number (%) of Subjects				
		P6 ACWY (N=89)	P11 ACWY (N=192)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 Tdap, ACWY (N=210)
SYSTEMIC						
Malaise	N	89	192	864	232	210
	ANY	13 (15%)	20 (10%)	81 (9%)	43 (19%)	28 (13%)
	MILD	8 (9%)	11 (6%)	51 (6%)	31 (13%)	18 (9%)
	MODERATE	4 (4%)	7 (4%)	19 (2%)	11 (5%)	7 (3%)
	SEVERE	1 (1%)	2 (1%)	11 (1%)	1 (<1%)	3 (1%)
Myalgia	N	89	192	864	232	210
	ANY	15 (17%)	37 (19%)	147 (17%)	37 (16%)	29 (14%)
	MILD	11 (12%)	25 (13%)	100 (12%)	24 (10%)	16 (8%)
	MODERATE	3 (3%)	10 (5%)	36 (4%)	11 (5%)	10 (5%)
	SEVERE	1 (1%)	2 (1%)	11 (1%)	2 (1%)	3 (1%)
Arthralgia	N	89	192	864	232	210
	ANY	6 (7%)	15 (8%)	69 (8%)	20 (9%)	17 (8%)
	MILD	6 (7%)	11 (6%)	52 (6%)	12 (5%)	14 (7%)
	MODERATE	0	0	14 (2%)	6 (3%)	3 (1%)
	SEVERE	0	4 (2%)	3 (<1%)	2 (1%)	0
Headache	N	89	192	864	232	210
	ANY	35 (39%)	58 (30%)	200 (23%)	74 (32%)	44 (21%)
	MILD	22 (25%)	40 (21%)	141 (16%)	41 (18%)	23 (11%)
	MODERATE	6 (7%)	10 (5%)	45 (5%)	29 (13%)	14 (7%)
	SEVERE	7 (8%)	8 (4%)	14 (2%)	4 (2%)	7 (3%)
Rash	N	0	0	864	232	210
	ANY	0	0	18 (2%)	4 (2%)	5 (2%)
	OTHER	0	0	7 (1%)	0	1 (<1%)
	URTICARIAL	0	0	11 (1%)	4 (2%)	4 (2%)

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 92

Summary of Reactogenicity on Days 1 to 7, MenACWY alone vs MenACWY after Tdap by Study and Gender
Ages 11-18

Gender: MALE

Reaction[1]		Number (%) of Subjects P6 ACWY (N=89)	P11 ACWY (N=192)	P13 ACWY (N=867)	P18 ACWY (N=232)	P18 Tdap, ACWY (N=210)
SYSTEMIC						
Fever (>= 38C)	N	89	192	859	232	210
	YES	1 (1%)	8 (4%)	14 (2%)	12 (5%)	11 (5%)
	NO	88 (99%)	184 (96%)	845 (98%)	220 (95%)	199 (95%)
OTHER						
Stayed Home	N	89	192	856	219	200
	YES	4 (4%)	7 (4%)	29 (3%)	15 (7%)	7 (4%)
	NO	85 (96%)	185 (96%)	827 (97%)	204 (93%)	193 (97%)
Analgesic Antipyretics	N	89	192	864	232	210
	YES	22 (25%)	14 (7%)	124 (14%)	32 (14%)	11 (5%)
	NO	67 (75%)	178 (93%)	740 (86%)	200 (86%)	199 (95%)
Temperature (C)	N	89	192	859	232	210
	<38 C	88 (99%)	184 (96%)	845 (98%)	220 (95%)	199 (95%)
	38 - 38.9 C	1 (1%)	5 (3%)	10 (1%)	8 (3%)	9 (4%)
	39.0 - 39.9 C	0	3 (2%)	4 (<1%)	4 (2%)	2 (1%)
	>= 40 C	0	0	0	0	0

[1] Most severe across all injections.

SOURCE: E:\MENACWY\DATAMART_NOV07\ISS\PROD\SAS\POSTINJ_MENVSTDAP_11_18SX.SAS(WARTERO) 10JUL08, 08:48 SAS.9.1 - PINJSUM_MENVSTDAP_11_18SX

Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ABDOMINAL ABSCESS	UMBILICAL ABSCESS	V59P13 (b) (6)
ABDOMINAL DISCOMFORT	GASTRO INTESTINAL UPSET	V59P13: (b) (6)
	PEPTIC DISTRESS	V59P13:
ABDOMINAL DISTENSION	ABDOMINAL DISTENSION	V59P17: (b) (6)
	LOW ABDOMINAL SWELLING	V59P17:
ABDOMINAL HERNIA	EPIGASTRIC HERNIA	V59P17 (b) (6)
ABDOMINAL PAIN	ABDOMINAL ACHE	V59P18: (b) (6)
	ABDOMINAL CRAMPS	V59P13:
	ABDOMINAL PAIN	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P11: V59P11:
		V59P11: V59P11: V59P11:
		V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P18: V59P18: V59P18:
		V59P18: V59P18: V59P18:
		V59P18: V59P6: (b) (6) V59P6: (b) (6)
		V59P6: (b) (6)
	COLIC	V59P17: (b) (6)
	GIRDLE PAIN	V59P17:
	INDETERMINATE ABDOMINAL PAIN	V59P6: (b) (6)

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
ABDOMINAL PAIN	PAIN ABDOMINAL	V59P11: (b) (6)
	PAIN IN ABDOMEN	V59P6 (b) (6)
	WAIST PAIN	V59P17: (b) (6)
ABDOMINAL PAIN LOWER	RIGHT LOWER QUADRANT ABDOMINAL PAIN	V59P6 (b) (6)
ABDOMINAL PAIN UPPER	EPIGASTRALGIA	V59P18: (b) (6)
	EPIGASTRALGY	V59P17:
	EPIGASTRIC PAIN	V59P11: V59P11: (b) (6) V59P17 (b) (6)
	GASTRALGIA	V59P11: V59P11:
	SHARP UPPER ABDOMINAL PAIN	V59P6: (b) (6)
	STOMACH ACHE	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P17: V59P18:
	STOMACH ACHE (PAIN)	V59P13:
	STOMACH CRAMPS	V59P13: V59P13 (b) (6), V59P13 (b) (6) V59P13:
	STOMACH PAIN	V59P13: V59P13 (b) (6)
	STOMACH PAINS	V59P13:
	STOMACHACHE	V59P13: V59P17 (b) (6) V59P17 (b) (6) V59P18:
ABORTION SPONTANEOUS	COMPLETE SPONTANEOUS ABORTION	V59P17: (b) (6) V59P17: (b) (6)
	SPONTANEOUS ABORTION	V59P17: V59P18:
ABORTION THREATENED	ABORTION THREATENING	V59P17 (b) (6)
ABSCESS	ABSCESS RELATED (SECONDARY TO) TO RHUS DERMATITIS	V59P13 (b) (6)

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ABSCESS LIMB	ABSCESS LEFT THIGH	V59P13: (b) (6)
	ABSCESS PRETIBIA	V59P13:
	ABSCESS RIGHT LEG	V59P13:
	PERIUNGUAL ABSCESS IN RIGHT FOOT	V59P17:
ABSCESS ORAL	HARD PALATE ABSCESS	V59P17 (b) (6)
ACCIDENTAL NEEDLE STICK	NEEDLE STICK INJURY	V59P17 (b) (6)
ACCIDENTAL OVERDOSE	ACCIDENTAL OVERDOSE OF LITHIUM	V59P13 (b) (6)
ACNE	ACNE	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P18: V59P18:
	ACNEIC EXACERBATION	V59P17:
	NODULAR ACNE	V59P6: (b) (6)
ACROCHORDON	SKIN TAG-ABDOMEN	V59P13 (b) (6)
ACUTE SINUSITIS	ACUTE SINUSITIS	V59P17 (b) (6) V59P17 (b) (6)
ACUTE TONSILLITIS	ACUTE TONSILLITIS	V59P17 (b) (6)
ADNEXA UTERI PAIN	OVARIES PAIN	V59P18: (b) (6) V59P18 (b) (6) V59P18 (b) (6) V59P18:
	OVARY PAIN	V59P18: V59P18 (b) (6) V59P18 (b) (6)
AGGRESSION	COMBATIVENESS	V59P13 (b) (6)
ALCOHOL ABUSE	ALCOHOL ABUSE	V59P6 (b) (6)
ALCOHOL POISONING	ALCOHOL INEBRIATION	V59P13 (b) (6)

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ALLERGIC OEDEMA	ALLERGIC REACTION-SWELLING (FACIAL/WHOLE BODY, NOT AT INJECTION SITE)	V59P13 (b) (6)
ALLERGY TO ANIMAL	ALLERGIC REACTION TO CATS	V59P13 (b) (6)
ALOPECIA	ALOPECIA	V59P13 (b) (6), V59P17 (b) (6)
AMNESIA	MEMORY LOSS	V59P18 (b) (6)
ANAEMIA	ANEMIA	V59P11: (b) (6) V59P13: (b) (6) V59P17 (b) (6) V59P17: V59P17: (b) (6)
ANAL FISSURE	ANAL FISSURE	V59P13 (b) (6)
ANGIOEDEMA	ANGIOEDEMA FACE ANGIOEDEMA GIANT URTICARIA	V59P17: (b) (6) V59P11: V59P17:
ANIMAL BITE	CAT BITE CAT BITE ON RIGHT LEG DOG BITE MONKEY BITES	V59P13: (b) (6) V59P13: V59P13: V59P17 (b) (6) V59P11:
ANKLE FRACTURE	DISLOCATION FRACTURE OF RIGHT ANKLE RIGHT ANKLE FRACTURE	V59P17: (b) (6) V59P13:
ANOREXIA	LOSS OF APPETITE	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)
ANXIETY	ANXIETY	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
ANXIETY	ANXIETY	V59P13: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P18:
	ANXIETY ATTACK	V59P13: V59P13 (b) (6)
APHTHOUS STOMATITIS	APHTHA	V59P11: (b) (6)
	APHTHOUS ULCER	V59P6: (b) (6)
	APHTHOUS ULCERATION	V59P13: (b) (6)
	ORAL APHTHOUS ULCERS	V59P13:
	ORAL MUCOSA APHTHA	V59P18:
APPENDICITIS	ACUTE APPENDICITIS	V59P18: (b) (6)
	APPENDICITIS	V59P6: (b) (6)
	GANGRENOUS APPENDICITIS	V59P13: (b) (6) V59P17 (b) (6)
APPLICATION SITE PRURITUS	THE PRURITUS IN THE ARM IN THE SITE OF APPLICATION OF THE PPD.	V59P17 (b) (6)
ARACHNOID CYST	CEREBELLAR ARACHNOID CYST	V59P6 (b) (6)
ARTHRALGIA	ACHE IN KNEE	V59P6: (b) (6)
	ANKLE PAIN	V59P17: (b) (6) V59P18: (b) (6)
	ARTHRALGIA	V59P11: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
ARTHRALGIA	ARTHRALGIA	V59P17: (b) (6) V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:
	ARTHRALGIA RIGHT KNEE	V59P17:
	BILATERAL HIP PAIN	V59P13:
	BILATERAL KNEE PAIN	V59P13:
	ELBOW PAIN	V59P13:
	HIP PAIN	V59P13: V59P13 (b) (6) V59P17 (b) (6)
	HIP/JOINT PAIN	V59P13:
	KNEE PAIN	V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P17: V59P17:
	LEFT COXALGIA	V59P17:
	LEFT ELBOW PAIN	V59P13:
	LEFT HIP PAIN	V59P13:
	LEFT KNEE PAIN	V59P13: V59P13 (b) (6)
	LEFT WRIST PAIN	V59P13:
	PAIN BEHIND LEFT KNEE	V59P13:
	PAIN LEFT WRIST	V59P13:
	POLYARTHRALGIA	V59P17:
	POLYARTICULAR JOINT PAIN	V59P13:
	RIGHT ANKLE PAIN	V59P13:
	RIGHT HIP PAIN	V59P13:
	RIGHT WRIST PAIN	V59P13:
	RT HIP PAIN	V59P13:
	SORE KNEE-RIGHT	V59P13:

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
ARTHRALGIA	TEMPOROMANDIBULAR JUNCTION ASSOCIATED PAIN-EXACERBATION	V59P17 (b) (6)
ARTHRITIS	ARTHRITIS	V59P13 (b) (6)
ARTHROPOD BITE	BUG BITE UNDER RT EYE	V59P13: (b) (6)
	BUG BITES ON NECK	V59P13:
	INSECT BITE	V59P13: V59P13 (b) (6) V59P18 (b) (6)
ARTHROPOD STING	BEE STING	V59P13: (b) (6)
	EDEMA CAUSED BY WASP STING	V59P17:
	WASP STING	V59P13:
ASTHENIA	ADYNAMIA	V59P17: (b) (6)
	ASTHENIA	V59P11: V59P11 (b) (6) V59P17 (b) (6)
	FATIGUE/MALAISE	V59P13:
	WEAKNESS	V59P13: V59P17 (b) (6)
ASTHMA	ALLERGIC ASTHMA	V59P11: (b) (6)
	ASTHMA	V59P11: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: (b) (6) V59P18: (b) (6)
		V59P18: V59P6: (b) (6)
	ASTHMA ATTACK	V59P13:
	ASTHMA EXACERBATION	V59P13:
	BRONCHIAL ASTHMA	V59P11:
	EXACERBATION OF ASTHMA	V59P13:
	MILD ASTHMA	V59P18: V59P18 (b) (6)
ASTHMA EXERCISE INDUCED	EXERCISE INDUCED ASTHMA	V59P13 (b) (6) V59P13 (b) (6)
ASTHMATIC CRISIS	ASTHMA CRISIS	V59P17 (b) (6), V59P17 (b) (6)

Note: Mappings done using MedDRA Version 10. Thesaurus.

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ATOPY	ALLERGY: ATOPIC	V59P18 (b) (6)
ATTENTION DEFICIT/HYPERACTIVITY DISORDER	ADHD	V59P13: (b) (6) V59P13: (b) (6)
	ATTENTION DEFICIT DISORDER	V59P13: V59P13: V59P6: (b) (6)
	ATTENTION DEFICIT HYPERACTIVITY DISORDER	V59P13: V59P13: V59P6:
	ATTENTION DEFICIT-HYPERACTIVITY DISORDER	V59P13:
AURICULAR SWELLING	LEFT POSTAURICULAR SWELLING	V59P6 (b) (6)
AXILLARY PAIN	AXILLA PAIN	V59P11: (b) (6)
	AXILLA SORENESS-LEFT ARM	V59P13:
	AXILLARY PAIN	V59P17:
	LEFT ARMPIT PAIN	V59P13:
	LEFT AXILLARY PAIN	V59P13:
BACK INJURY	BACK INJURY	V59P13: (b) (6) V59P13 (b) (6)
	LUMBAR SPRAIN	V59P13:
	LUMBAR STRAIN	V59P13:
	MUSCLE SPRAIN-BACK	V59P13:
BACK PAIN	BACK ACHE	V59P11: (b) (6) V59P13: (b) (6)
	BACK PAIN	V59P11: V59P13: V59P13 (b) (6)
		V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P18:

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
BACK PAIN	BACK PAIN (RELATED TO #4 DIAG)	V59P13: (b) (6)
	BACK SORENESS	V59P13:
	BACKACHE	V59P13:
	LOW BACK PAIN	V59P13:
	LOWER BACK PAIN	V59P13:
	LUMBAGO	V59P17:
		V59P17:
	LUMBALGIA	V59P17:
	LUMBAR BACK PAIN	V59P17:
	LUMBAR PAIN	V59P17:
		V59P17:
		V59P17:
	MECHANICAL LUMBAGO	V59P17:
	SACRAL PAIN AFTER FALL	V59P13:
BACTERIAL INFECTION	BACTERIAL INFECTION	V59P13 (b) (6)
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION	STREPTOCOCCUS GROUP A	V59P13 (b) (6)
BILIARY COLIC	BILIARY COLIC	V59P17 (b) (6)
BIPOLAR DISORDER	BI-POLAR DISORDER	V59P13 (b) (6)
BLEPHARITIS	BLEPHARITIS	V59P17: (b) (6)
	RIGHT BLEPHARITIS	V59P17:
BLOOD CHOLESTEROL INCREASED	INCREASED CHOLESTEROL	V59P13 (b) (6)
BLOOD POTASSIUM DECREASED	LOW POTASSIUM	V59P13 (b) (6)
BLOOD PRESSURE INCREASED	ELEVATED BLOOD PRESSURE	V59P13 (b) (6)

Note: Mappings done using MedDRA Version 10. Thesaurus.

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
BODY TINEA	RINGWORM ON FACE	V59P13 (b) (6)
BREAST CELLULITIS	CELLULITIS IN BREAST	V59P17 (b) (6)
BREAST MASS	MAMMARY NODULE	V59P17 (b) (6)
BREAST NEOPLASM	PHYLLODES TUMOR	V59P17 (b) (6)
BREAST PAIN	MASTALGIA MASTODYNIA PAIN AT RIGHT BREAST	V59P17: (b) (6) V59P13: V59P17:
BRONCHIAL HYPERREACTIVITY	BRONCHIAL HYPERREACTIVITY REACTIVE AIRWAY DISEASE	V59P17: (b) (6) V59P13: V59P13 (b) (6) , V59P13 (b) (6)
BRONCHITIS	ACUTE BRONCHITIS	V59P11: (b) (6) V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: (b) (6) V59P17: (b) (6) V59P17:
	BRONCHITIS	V59P11: V59P11: (b) (6) V59P11: (b) (6) V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P6: (b) (6)
BRONCHITIS VIRAL	VIRAL BRONCHITIS	V59P13 (b) (6)
BRONCHOPNEUMONIA	BRONCHOPNEUMONIA	V59P11 (b) (6) V59P17 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
BRONCHOSPASM	BRONCHOSPASM	V59P13: (b) (6) V59P13 (b) (6), V59P17 (b) (6) V59P18:
	EXERCIZE INDUCED BRONCHOSPASMS	V59P13:
BURNING SENSATION	ARM BURNING SENSATION	V59P17: (b) (6)
	BURN SENSATION	V59P17:
	BURNING	V59P11:
BURNS SECOND DEGREE	2ND DEGREE BURNS TO RIGHT ARM	V59P13 (b) (6)
BURSITIS	BURSITIS AT RIGHT METATARSUS	V59P11: (b) (6)
	LEFT HAND JOINT BURSITIS	V59P18:
	RIGHT PREPATELLAR BURSITIS	V59P13:
CALCULUS URETERIC	URETERAL CALCULUS	V59P13 (b) (6)
CANDIDIASIS	THRUSH	V59P11 (b) (6)
CARDIAC MURMUR	HEART MURMUR	V59P13 (b) (6)
CARPAL TUNNEL SYNDROME	CARPAL TUNNEL SYNDROME	V59P13: (b) (6) V59P13 (b) (6) V59P17 (b) (6)
	EXACERBATION OF CARPAL TUNNEL SYNDROME	V59P17:
CELLULITIS	CELLULITIS	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P18:
	CELLULITIS BILATERAL ANTERIOR LEGS	V59P6: (b) (6)
	CELLULITIS GREAT TOE	V59P13: (b) (6)
	CELLULITIS LEFT ARM	V59P13:
	CELLULITIS LEFT FLANK	V59P13:
	CELLULITIS LEFT GREAT TOE	V59P13:
	CELLULITIS R 4TH TOE	V59P6: (b) (6)

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...Continued from previous page		
CELLULITIS	CELLULITIS RIGHT ARM	V59P13: (b) (6)
	FACIAL CELLULITIS	V59P17:
	LEFT FOOT CELLULITIS	V59P17:
	RIGHT ARM CELLULITIS	V59P17: V59P18 (b) (6)
CHEST DISCOMFORT	CHEST PRESSURE (DURING EXERCISE	V59P13: (b) (6)
	PRESSURE IN CHEST	V59P13:
CHEST INJURY	CHEST INJURY	V59P13 (b) (6)
CHEST PAIN	CHEST PAIN	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P18:
	CHEST PAIN (ON THE RIGHT)	V59P11:
	CHEST PAINS	V59P13:
	PRECORDIAL CHEST PAIN	V59P13:
CHILLS	CHILLS	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6)
	CHILLS GENERAL SYMPTOMS	V59P18: (b) (6)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	COPD (CHRONIC OBSTRUCTIVE PULMONARY)	V59P17 (b) (6)
CIRCULATORY COLLAPSE	COLLAPSE	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
CLAVICLE FRACTURE	BROKEN COLLAR BONE	V59P13: (b) (6)
	FRACTURE OF CLAVICLE	V59P13:
	LEFT CLAVICLE FRACTURE	V59P13:
	RIGHT CLAVICLE FRACTURE	V59P13:
COLITIS	COLITIS	V59P17: (b) (6) V59P18 (b) (6) V59P18 (b) (6) V59P18:
CONCUSSION	CLOSED HEAD INJURY GRADE 2 CONCUSSION	V59P6 (b) (6)
	CONCUSSION	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P6: (b) (6)
	GRADE 3 CONCUSSION	V59P13:
	SLIGHT CONCUSSION	V59P13:
CONJUNCTIVAL PIGMENTATION	EYE SPOT (PIGMENTED PORTION OF CONJUNCTIVA)	V59P18 (b) (6)
CONJUNCTIVITIS	BILATERAL CONJUNCTIVITIS	V59P6: (b) (6)
	CONJUNCTIVITIS	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P17: V59P17: (b) (6) V59P18: (b) (6) V59P18: V59P6: (b) (6) V59P6: (b) (6)
	CONJUNCTIVITIS-R EYE	V59P13:
CONJUNCTIVITIS ALLERGIC	ATOPIC CONJUNCTIVITIS	V59P17 (b) (6)
CONJUNCTIVITIS BACTERIAL	BACTERIAL CONJUNCTIVITIS	V59P17 (b) (6) V59P17 (b) (6)
CONSTIPATION	CHRONIC CONSTIPATION	V59P6: (b) (6)
	CONSTIPATION	V59P11: (b) (6) V59P13: (b) (6) V59P17 (b) (6) V59P17: V59P6:
CONTUSION	BADLY BRUISED FINGER	V59P6 (b) (6)

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CONTUSION	BRUISED BONE-RIGHT HAND	V59P13: (b) (6)
	BRUISED FOOT	V59P13:
	BRUISED RIBS	V59P13:
	CONTUSION OF THE RIBS	V59P13:
	CONTUSIONS	V59P13: V59P13 (b) (6)
	CONTUSIONS, NECK, SCALP AND FACE	V59P13:
	HEAD CONTUSION	V59P6: (b) (6)
	LEFT KNEE BONE BRUISE	V59P13: (b) (6)
	LEFT LEG CONTUSIONS	V59P13:
	MULTIPLE CONTUSIONS	V59P13:
	MUSCOLO - SKELETAL BRUISING RIGHT LEG	V59P11:
	RIGHT ANKLE CONTUSION	V59P13:
	RIGHT KNEE CONTUSION	V59P13:
CONVERSION DISORDER	PSEUDOSEIZURE DISORDER	V59P13 (b) (6)
CONVULSION	POSSIBLE SEIZURE	V59P13 (b) (6)
COSTOCHONDRITIS	COSTOCHONDRITIS	V59P13 (b) (6) V59P13 (b) (6) V59P17 (b) (6)
COUGH	COUGH	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P13: V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
COUGH	COUGH	V59P17: (b) (6) V59P17: (b) (6) V59P18: (b) (6) V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: V59P6: V59P6:
	HACKING COUGH	V59P11: (b) (6)
	HARD COUGH	V59P13:
CUSHING'S SYNDROME	CUSHING'S SYNDROME	V59P18 (b) (6)
CYST REMOVAL	GANGLION CYST REMOVAL	V59P13 (b) (6)
CYSTITIS	BLADDER INFECTION	V59P13: (b) (6)
	CYSTITIS	V59P17: V59P17 (b) (6) V59P17 (b) (6)
DEEP VEIN THROMBOSIS	RIGHT DEEP VEIN THROMBOSIS	V59P17 (b) (6)
DEFICIENCY ANAEMIA	NUTRITIONAL ANEMIA	V59P17 (b) (6)
DEHYDRATION	DEHYDRATION	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)
DENGUE FEVER	DENGUE	V59P18 (b) (6)
DEPRESSION	ACUTE DEPRESSION	V59P13: (b) (6)
	DEPRESSION	V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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DEPRESSION	DEPRESSION	V59P17: (b) (6) V59P17: (b) (6) V59P6 (b) (6) V59P6 (b) (6) V59P6: (b) (6)
	DEPRESSION (WORSENING OF CONDITION)	V59P13: (b) (6)
	EXACERBATION OF DEPRESSION	V59P13:
	INCREASED DEPRESSION	V59P13:
	MODERATE DEPRESSION	V59P13:
	WORSENED DEPRESSION	V59P13:
	WORSENING OF DEPRESSION	V59P13: V59P13 (b) (6)
DEPRESSION SUICIDAL	DEPRESSION WITH SUICIDAL IDEATION	V59P13 (b) (6)
DERMAL CYST	EPIDERMAL CYST-CHEST	V59P13: (b) (6)
	SEBACEOUS CYST	V59P13:
DERMATITIS	DERMATITIS	V59P13: (b) (6)
	THREE AND FOUR LEFT FINGER DERMATITIS	V59P18:
DERMATITIS ALLERGIC	ALLERGIC DERMATITIS	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6)
	ALLERGY-RASH	V59P18:
	SKIN ALLERGY	V59P18: V59P18 (b) (6)
DERMATITIS ATOPIC	ATOPIC DERMATITIS	V59P13 (b) (6) V59P17 (b) (6)
DERMATITIS CONTACT	CONTACT DERMATITIS	V59P13: (b) (6) V59P13 (b) (6) V59P13 (b) (6) V59P17:
	CONTACT DERMATITIS RIGHT ARM	V59P13:
	CONTACT DERMATITIS RIGHT FOREARM	V59P13:
	POISON IVY	V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13:

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DERMATITIS CONTACT	POISON IVY	V59P13: (b) (6) V59P13: (b) (6) V59P13 (b) (6) V59P13: V59P13:
	POISON IVY BOTH LEGS	V59P13:
	POISON OAK	V59P13:
	RHUS DERMATITIS	V59P13:
DIABETES MELLITUS	INSIDIOUS DIABETES	V59P18 (b) (6)
DIARRHOEA	ACUTE DIARRHEA	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P17:
	DIARRHEA	V59P11: V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P11: V59P13: V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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DIARRHOEA	DIARRHEA	V59P18 (b) (6) V59P6: (b) (6) V59P6: (b) (6)
	DIARRHOEA	V59P11 V59P11: V59P11:
	LOOSE STOOLS	V59P13
DISCOMFORT	SPORTS-RELATED DISCOMFORT	V59P13 (b) (6)
DISLOCATION OF STERNUM	STERNOMANUBRIUM DISLOCATION	V59P13 (b) (6)
DISSOCIATIVE DISORDER	DISSOCIATIVE BEHAVIOR	V59P18 (b) (6)
DISTURBANCE IN ATTENTION	DIFFICULTY CONCENTRATING	V59P6 (b) (6)
DIVERTICULUM INTESTINAL	DIVERTICULOSIS, COLON	V59P13 (b) (6)
DIZZINESS	DIZZINESS	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: (b) (6) V59P13: V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P18: V59P18: V59P6 (b) (6)
	DIZZY	V59P13: V59P13: V59P13: (b) (6)
		V59P13:
	DIZZY FOR 2 MINUTES	V59P13:

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DIZZINESS	GIDDINESS	V59P11: (b) (6) V59P17 (b) (6)
	INTERMITTENT DIZZINESS	V59P13:
	LIGHT HEADED	V59P13: V59P13 (b) (6)
	LIGHT-HEADED	V59P13:
	LIGHTHEADED	V59P13:
	LIGHTHEADEDNESS	V59P13:
DRUG HYPERSENSITIVITY	ALLERGY TO SULFONAMIDES	V59P13: (b) (6)
	ALLERGY TO TORADOL	V59P13:
	DRUG REACTION TO PHENTERMINE	V59P13:
DRY MOUTH	DRY MOUTH	V59P13: (b) (6)
	XEROSTOMIA	V59P17:
DRY SKIN	DRY SKIN ON SCALP	V59P13 (b) (6)
DRY THROAT	DRY THROAT	V59P13 (b) (6)
DYSLIPIDAEMIA	DYSLIPIDEMIA	V59P13: (b) (6) V59P17: (b) (6) V59P17 (b) (6)
		V59P17: V59P17:
DYSMENORRHOEA	DYSMENORRHEA	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6)
		V59P13: V59P13: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P18: V59P18: V59P18:

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DYSMENORRHOEA	DYSMENORRHEA	V59P18: (b) (6)	V59P18: (b) (6)	V59P18: (b) (6)
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	
	DYSMENORRHOEA	V59P18:		
	GREATLY INCREASED MENSTRUAL PAIN	V59P13:		
	MENSTRUAL CRAMPS	V59P13:	V59P13: (b) (6)	V59P13: (b) (6)
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P6: (b) (6)	V59P6: (b) (6)	V59P6: (b) (6)
		V59P6:		
	MENSTRUAL CRAMPS.	V59P17: (b) (6)		
	MENSTRUAL PAIN	V59P11:	V59P18: (b) (6)	V59P18: (b) (6)
		V59P18:	V59P18: (b) (6)	V59P18: (b) (6)
		V59P18:	V59P18:	
DYSPEPSIA	DYSPEPSIA	V59P17: (b) (6)	V59P17: (b) (6)	V59P17: (b) (6)
		V59P17:	V59P17:	V59P17:
	HEART BURN	V59P13:		
	HEARTBURN	V59P13:		
	INDIGESTION	V59P17:	V59P17 (b) (6)	

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DYSPEPSIA	INTERMITTENT HEARTBURN	V59P13 (b) (6)
DYSPHONIA	DYSPHONIA	V59P17 (b) (6)
DYSPNOEA	DIFFICULTY BREATHING	V59P13: (b) (6)
	DYSPNEA	V59P11: V59P13 (b) (6) V59P13 (b) (6)
		V59P17:
	SHORT OF BREATH	V59P13:
	SHORTNESS OF BREATH	V59P13: V59P13 (b) (6)
DYSTONIA	ACUTE DYSTONIC REACTION	V59P13 (b) (6)
EAR INFECTION	EAR INFECTION	V59P13: (b) (6)
	L EAR INFECTION (EXTERNAL)	V59P13:
	LEFT OTITIS	V59P17:
	OTITIS	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P11: V59P11:
		V59P17:
	OTITIS LEFT	V59P11:
	OTITIS MEDIA, EXTERNA	V59P13:
	OTITIS, RIGHT	V59P18:
EAR LOBE INFECTION	INFECTION LEFT EAR LOBE	V59P13 (b) (6)
EAR PAIN	EAR ACHE	V59P13: (b) (6)
	EAR PAIN	V59P13: V59P13 (b) (6) V59P6 (b) (6)
	EAR PAIN (RT)	V59P13:
	EARACHE	V59P13: V59P17 (b) (6)
	LEFT EAR PAIN	V59P17:

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EAR PAIN	OTALGIA	V59P11: (b) (6) V59P11 (b) (6) V59P11 (b) (6)
	OTALGIA (LEFT)	V59P13: V59P17:
	RIGHT EAR PAIN	V59P17:
ECCHYMOSIS	ECCHYMOSIS	V59P17 (b) (6) V59P17 (b) (6)
ENCEPHALOPATHY	ENCEPHALOPATHY	V59P13 (b) (6)
ENDODONTIC PROCEDURE	ENDODONTIA (TREATMENT FOR DISEASE OF THE DENTAL PULP)	V59P18 (b) (6)
ENDOSCOPY	ENDOSCOPY	V59P13 (b) (6)
ENTERITIS INFECTIOUS	INTESTINAL INFECTION	V59P18 (b) (6)
ENTEROBIASIS	PINWORMS	V59P13 (b) (6)
ENTEROCOLITIS	ENTEROCOLITIS	V59P18 (b) (6)
ENTHESOPATHY	ENTHESOPATHY OF KNEE	V59P13 (b) (6)
EPICONDYLITIS	TENNIS ELBOW	V59P13: (b) (6)
	TENNIS ELBOW (RT)	V59P13:
EPILEPSY	PRIMARY GENERALIZED IDIOPATHIC EPILEPSY	V59P13 (b) (6)
EPIPHYSIOLYSIS	RIGHT HIP SLIPPED CAPITAL FEMORAL EPIPHYSIS	V59P13 (b) (6)
EPISTAXIS	EPISTAXIS	V59P11 (b) (6) V59P13 (b) (6) V59P17 (b) (6)

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EPISTAXIS	EPISTAXIS	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6)
	MILD RHINORRHAGIA	V59P11:
	NOSE BLEED	V59P6: (b) (6)
	NOSE BLEEDS	V59P13: (b) (6)
	RECURRENT EPISTAXIS	V59P6: (b) (6) V59P6 (b) (6)
ERECTILE DYSFUNCTION	ERECTILE DYSFUNCTION	V59P13 (b) (6)
ERYTHEMA	ERYTHEMA	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P18: V59P18: V59P18:
		V59P18:
	ERYTHEMA LEFT ARM	V59P18:
	ERYTHEMA LEFT UPPER ARM	V59P6: (b) (6)
	ERYTHEMA RIGHT ARM	V59P18: (b) (6)
	LEFT ELBOW ERYTHEMA	V59P17:
ERYTHEMA INFECTIOSUM	FIFTH DISEASE	V59P13: (b) (6)
	PARVOVIRUS B19 INFECTION	V59P13:
EUSTACHIAN TUBE DYSFUNCTION	EUSTACHIAN TUBE DYSFUNCTION	V59P13 (b) (6)
EXCORIATION	ABRASION LEFT ELBOW	V59P13: (b) (6)
	ABRASION LEFT KNEE	V59P13:
	ABRASION RIGHT TIBIA	V59P13:
	ABRASION TO TRUNK OF BODY	V59P13:

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...Continued from previous page		
EXCORIATION	ABRASIONS ON BACK	V59P13: (b) (6)
	INFECTED KNEE ABRASIONS	V59P13:
	LEFT KNEE ABRASION	V59P13:
EXOSTOSIS	CALCANEAL APOPHYSITIS	V59P13: (b) (6)
	HEEL SPURS	V59P13:
EXTERNAL EAR CELLULITIS	CELLULITIS RIGHT EAR	V59P13 (b) (6)
EXTRASYSTOLES	EXTRASYSTOLE	V59P17 (b) (6)
EYE ALLERGY	EYE ALLERGY	V59P18 (b) (6)
EYE DISCHARGE	RUNNY DISCHARGE RIGHT EYE	V59P13 (b) (6)
EYE INFECTION	EYE INFECTION	V59P13 (b) (6) V59P18 (b) (6)
EYE INFECTION TOXOPLASMAL	TOXOPLASMOSIS RIGHT EYE	V59P17 (b) (6)
EYE INJURY	RIGHT EYE INJURY	V59P13 (b) (6)
EYE IRRITATION	EYE IRRITATION	V59P13: (b) (6)
	EYES IRRITATION	V59P17:
EYE PAIN	EYE PAIN	V59P13: (b) (6)
	LEFT EYE PAIN	V59P13:
	RETROOCULAR PAIN	V59P17:
EYE PRURITUS	ITCHY EYES	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
EYE SWELLING	SWELLING EYES	V59P18: (b) (6)
	SWOLLEN RIGHT EYE	V59P13:
FACE INJURY	FACIAL INJURIES	V59P13 (b) (6)
FACIAL BONES FRACTURE	BROKEN NOSE	V59P13 (b) (6)
FACIAL NEURALGIA	ODONTONEURALGIA	V59P11 (b) (6)
FACIAL PALSY	BELL'S PALSY	V59P17 (b) (6)
FALL	FALL OUT OF HIS OWN HIGHT	V59P17: (b) (6)
	MUSCLE SPASMS IN KNEES DUE TO FALL	V59P13:
	TRAUMA TO RT. FIBULA + RT. ANKLE SECONDARY TO FALL	V59P13:
FATIGUE	FATIGUE	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P6: (b) (6) V59P6: (b) (6)
	TIREDNESS	V59P13: (b) (6) V59P13: (b) (6) V59P17 (b) (6)
	TIREDNESS (FATIGUE)	V59P13:
FEELING HOT	HEAT SENSATION	V59P17: (b) (6)
	VACCINATED ARM FEELS " WARM" FROM SHOULDER TO ELBOW	V59P6 (b) (6)
	WARM SENSATION	V59P17: (b) (6) V59P17 (b) (6)
FEMUR FRACTURE	SALTER-HARRIS II FRACTURE DISTAL LEFT FEMUR	V59P6 (b) (6)
FIBROADENOMA OF BREAST	FIBROADENOMA AT LEFT BREAST	V59P18 (b) (6)
FIBROCYSTIC BREAST DISEASE	BENIGN FIBROCYSTIC BREAST MASS-RIGHT	V59P6 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
FINGER AMPUTATION	PARTIAL AMPUTATION OF ONE LEFT HAND'S FINGER	V59P11 (b) (6)
FLUSHING	FACIAL FLUSHING	V59P13: (b) (6)
	FLUSHES	V59P17:
	FLUSHING	V59P17:
	FLUSHING OF FACE	V59P13:
FOLLICULITIS	FOLLICULITIS LEGS	V59P13 (b) (6)
FOOD ALLERGY	ALIMENTARY ALLERGY	V59P18 (b) (6)
FOOD POISONING	ALIMENTARY INTOXICATION	V59P17 (b) (6)
	FOOD POISONING	V59P17
FOOT FRACTURE	BROKEN 5TH METATARSAL LEFT FOOT	V59P13: (b) (6)
	BROKEN FOOT	V59P13:
	BROKEN L GREAT TOE	V59P13:
	BROKEN RIGHT GREAT TOE	V59P13:
	FRACTURE LEFT GREAT TOE	V59P13:
	FRACTURE OF LEFT FOOT	V59P13:
	FRACTURE RIGHT FOOT	V59P13:
	FRACTURED R TOE	V59P13:
	METATARSAL FRACTURES # 2, 3, 4 RIGHT FOOT	V59P6 (b) (6)
	RIGHT TOE FRACTURE	V59P17: (b) (6)
FRACTURED COCCYX	COCCYGEAL FRACTURE	V59P11: (b) (6)
	COCCYX FRACTURE	V59P17:
FUNGAL INFECTION	EAR MYCOSIS	V59P18: (b) (6)
	YEAST INFECTION	V59P13: V59P13: (b) (6) V59P13 (b) (6)
		V59P13: V59P13:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
FUNGAL SKIN INFECTION	DERMATOMYCOSIS	V59P17: (b) (6)
	FACIAL DERMATOMYCOSIS	V59P17:
GAIT DISTURBANCE	DISTURBANCE OF GAIT	V59P13 (b) (6)
GALLBLADDER POLYP	GALLBLADDER POLYPS	V59P13 (b) (6)
GASTRIC ULCER	GASTRIC ULCER	V59P17 (b) (6)
GASTRITIS	ACUTE GASTRITIS	V59P17: (b) (6) V59P17 (b) (6)
	CHRONIC GASTRITIS EXACERBATION	V59P17:
	GASTRITIS	V59P17: V59P17: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P18: V59P18:
		V59P18: V59P18: V59P18:
GASTROENTERITIS	ACUTE GASTROENTERITIS	V59P17: (b) (6)
	GASTROENTERIC SYNDROME	V59P17: V59P17: (b) (6)
	GASTROENTERITIS	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P11: V59P11:
		V59P11: V59P11: V59P13:
		V59P13: V59P13: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P18:
		V59P18: V59P18: V59P18:
		V59P6: (b) (6) V59P6: (b) (6)

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GASTROENTERITIS VIRAL	GASTROINTESTINAL VIRUS	V59P13: (b) (6)
	STOMACH VIRUS	V59P13:
	VIRAL GASTROENTERITIS	V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P17:
	VIRAL INFECTION INTESTINAL	V59P13:
GASTROINTESTINAL INFLAMMATION	INTESTINAL INFLAMMATION	V59P17 (b) (6)
GASTROINTESTINAL PAIN	GASTROINTESTINAL CRAMPING	V59P13 (b) (6)
GASTROOESOPHAGEAL REFLUX DISEASE	ACID REFLUX	V59P18: (b) (6)
	GASTRIC REFLUX	V59P18:
	GASTROESOPHAGEAL DISEASE	V59P13:
	GASTROESOPHAGEAL REFLUX	V59P13: V59P13: (b) (6)
	GASTROESOPHAGEAL REFLUX DISEASE	V59P13: V59P13: V59P13 (b) (6)
		V59P6: (b) (6)
	REFLUX	V59P13: (b) (6)
GENERALISED OEDEMA	EDEMA GENERALIZED	V59P17 (b) (6)
GENITAL HERPES	HERPES SIMPLEX VIRUS, GENITAL	V59P13 (b) (6)
GINGIVAL PAIN	GUM PAIN	V59P18: (b) (6)
	PAIN IN GUMS	V59P17:
	SORE GUMS	V59P13:
GINGIVITIS	GINGIVITIS	V59P13 (b) (6)
GLOSSODYNIA	SORE TONGUE	V59P13 (b) (6)
GRAND MAL CONVULSION	SEIZURE, GRAND MAL	V59P13 (b) (6)
GUN SHOT WOUND	GUNSHOT IN LEFT KNEE	V59P17 (b) (6)

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GYNAECOMASTIA	GYNECOMASTIA-BENIGN	V59P13 (b) (6)
HAEMATURIA	HEMATURIA	V59P17 (b) (6)
HAEMORRHOIDS	HEMORRHOIDAL PAIN	V59P17: (b) (6)
	HEMORRHOIDS	V59P13:
HALLUCINATION, AUDITORY	COMMAND AUDITORY HALLUCINATIONS	V59P6 (b) (6)
HAND FRACTURE	AVULSION FRACTURE-RIGHT 5TH FINGER	V59P13: (b) (6)
	BROKEN LITTLE FINGER	V59P6: (b) (6)
	CLOSED FRACTURE TO MIDDLE FINGER	V59P13: (b) (6)
	FIRST FINGER RIGHT FRACTURE	V59P18:
	FRACTURE LEFT LITTLE FINGER	V59P13:
	FRACTURE RING FINGER LEFT HAND	V59P13:
	LEFT HAND 5TH DIGIT PHALANX FRACTURE	V59P13:
	LEFT THUMB FRACTURE	V59P6: (b) (6)
	METACARPAL FRACTURE	V59P13: (b) (6)
	RIGHT THUMB FRACTURE	V59P13:
HEAD INJURY	HEAD INJURY	V59P13: (b) (6) V59P6 (b) (6)
	HEAD TRAUMA	V59P17:
	MILD CRANEOENCEPHALIC TRAUMA WITH WOUND IN FRONTAL SURFACE OF HEAD	V59P17:
	MILD HEAD INJURY	V59P17 (b) (6)
HEADACHE	CEPHALEA	V59P17: (b) (6)
	CEPHALGIA	V59P11:
	HEADACHE	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P11: V59P11:
		V59P11: V59P11: V59P11:

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HEADACHE	HEADACHE	V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:
		V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:
		V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:

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HEADACHE	HEADACHE	V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:
		V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:
		V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:

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HEADACHE	HEADACHE	V59P18: (b) (6) V59P18: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: V59P6: V59P6: V59P6: V59P6: V59P6: V59P6: V59P6: V59P6: V59P6:
	HEADACHES	V59P13: (b) (6) V59P13: (b) (6) V59P6: (b) (6)
	LEFT POSTAURICULAR PAIN	V59P6 (b) (6)
	MILD HEADACHE	V59P17: (b) (6)
	SEVERE HEADACHE	V59P11: V59P17 (b) (6)
	SYSTEMIC REACTION (HEADACHE)	V59P17:
	WORSENING HEADACHES	V59P13:
HEART RATE INCREASED	INCREASE HEART RATE	V59P13 (b) (6)
HEAT EXHAUSTION	HEAT EXHAUSTION	V59P13 (b) (6)
HEAT STROKE	HEAT STROKE	V59P11 (b) (6)
HELICOBACTER GASTRITIS	H. PYLORI DUODENAL ULCER	V59P13: (b) (6)
	HELICOBACTER PYLORI PEPTIC ULCER	V59P13:
HELICOBACTER INFECTION	HELICOBACTER PYLORI INFECTION	V59P13 (b) (6)
HEPATITIS	HEPATITIS, UNSPECIFIED	V59P6 (b) (6)
HEPATOMEGALY	HEPATOMEGALY	V59P13 (b) (6)
HERNIA	HERNIA	V59P17 (b) (6)

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HERPES ZOSTER	HERPES ZOSTER SHINGLES	V59P17: (b) (6) V59P17: (b) (6) V59P17: (b) (6) V59P13: V59P13: V59P13:
HIV INFECTION	HIV	V59P17 (b) (6)
HORDEOLUM	HORDEOLUM	V59P17 (b) (6)
HOT FLUSH	HOT FLASHES	V59P13 (b) (6)
HOUSE DUST ALLERGY	DUST ALLERGY	V59P18 (b) (6)
HUNGER	EXCESSIVE HUNGER	V59P13 (b) (6)
HYPERCHLORHYDRIA	ACIDITY OF THE STOMACH GASTRIC ACIDITY	V59P17: (b) (6) V59P17: V59P18 (b) (6)
HYPERCHOLESTEROLAEMIA	HYPERCHOLESTEROLEMIA	V59P13: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P17:
HYPERHIDROSIS	DIAPHORESIS DIAPHORETIC HYPERHIDROSIS INCREASED SWEATING	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P17: V59P13: V59P13: V59P17:
HYPERINSULINISM	HYPERINSULINISM	V59P13 (b) (6)
HYPERLIPIDAEMIA	HYPERLIPIDEMIA	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)
HYPERSENSITIVITY	ALLERGIC REACTION ALLERGIC REACTION TO SEVEDOL	V59P6: (b) (6) V59P17: (b) (6)

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HYPERSENSITIVITY	ALLERGY	V59P13: (b) (6) V59P18: V59P18: (b) (6) V59P18: V59P18: V59P18: (b) (6) V59P18:
	ALLERGY SYMPTOMS	V59P13: V59P13:
	EXACERBATION OF ALLERGY	V59P18:
HYPERTENSION	ARTERIAL HYPERTENSION	V59P17: (b) (6)
	HIGH BLOOD PRESSURE	V59P13:
	HYPERTENSION	V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P17: V59P17: V59P17:
		V59P17:
	HYPERTENSION EPISODE	V59P17:
HYPERTENSIVE CRISIS	HYPERTENSION CRISIS	V59P17: (b) (6) V59P17 (b) (6)
	HYPERTENSIVE CRISIS	V59P17:
HYPERVENTILATION	HYPERVENTILATION	V59P13 (b) (6)
HYPOACUSIS	HEARING LOSS R EAR	V59P13 (b) (6)
HYPOAESTHESIA	NUMBNESS ARMS & LEGS	V59P13: (b) (6)
	NUMBNESS IN LEFT ARM	V59P13:
	RIGHT FOOT NUMBNESS STATUS POST RIGHT ACL SURGERY	V59P13:
HYPOAESTHESIA FACIAL	NUMBNESS ON LEFT JAW LINE	V59P6 (b) (6)
HYPOKALAEMIA	HYPOKALEMIA	V59P13 (b) (6)
HYPOTENSION	HYPOTENSION	V59P17 (b) (6)

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HYPOTHYROIDISM	HYPOTHYROIDISM	V59P13: (b) (6) V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17:
HYSTERECTOMY	HYSTERECTOMY	V59P17 (b) (6) V59P17 (b) (6)
IMPETIGO	IMPETIGO	V59P11: (b) (6) V59P13 (b) (6) V59P13 (b) (6) V59P18:
INCREASED APPETITE	INCREASE APPETITE INCREASED APPETITE	V59P17: (b) (6) V59P17:
INDURATION	INDURATION	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6)
INFECTION PARASITIC	PARASITOSIS	V59P17 (b) (6)
INFECTIOUS MONONUCLEOSIS	EBV MONONUCLEOSIS INFECTIOUS MONONUCLEOSIS MONONUCLEOSIS	V59P6: (b) (6) V59P13: (b) (6) V59P13: V59P13 (b) (6) V59P13 (b) (6)
INFLUENZA	FLU	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P11: V59P11: V59P17: V59P17: (b) (6) V59P17: V59P18: (b) (6) V59P18: (b) (6) V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6)

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
INFLUENZA	FLU SYMPTOMS	V59P17: (b) (6) V59P6: (b) (6)
	FLU SYNDROME	V59P11: V59P11: V59P11: (b) (6)
		V59P11: V59P11: V59P11:
		V59P11: V59P11: V59P11:
		V59P11: V59P11: V59P11:
	INFLUENZA	V59P13: V59P17 (b) (6)
	INFLUENZA SYNDROME	V59P11: V59P11: (b) (6)
	SEVERE FLU	V59P18:
	SYNDROME FLU	V59P11: V59P11 (b) (6) V59P11 (b) (6)
INFLUENZA LIKE ILLNESS	FLU LIKE SYMPTOMS	V59P13: (b) (6) V59P13: (b) (6)
	FLU LIKE SYNDROME	V59P17: V59P17: V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
	FLU-LIKE SYMPTOMS	V59P13:
INGROWING NAIL	INGROWN TOE NAIL-LEFT GREAT	V59P6: (b) (6)
	INGROWN TOE NAIL-RIGHT GREAT TOE	V59P13: (b) (6)
	INGROWN TOENAIL	V59P17:
	WORSENING OF INGROWN TOENAIL	V59P13:
INJECTION SITE ANAESTHESIA	NUMBNESS AT INJECTION SITE	V59P13 (b) (6)
INJECTION SITE BRUISING	BRUISE AROUND INJECTION SITE	V59P13: (b) (6)
	BRUISE AT INJECTION SITE	V59P13: V59P13 (b) (6) V59P13 (b) (6)
	BRUISE AT INJECTION SITE 3 CM	V59P13:
	BRUISING @ INJECTION SITE	V59P13:
	BRUISING AT INJECTION SITE	V59P13: V59P6 (b) (6)

Note: Mappings done using MedDRA Version 10. Thesaurus.

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
INJECTION SITE ERYTHEMA	ERYTHEMA @ INJECTION SITE	V59P13: (b) (6) V59P13: (b) (6)
	ERYTHEMA AT INJECTION SITE	V59P17: V59P17: V59P17 (b) (6)
		V59P17: V59P17: V59P17
		V59P6: (b) (6) V59P6: (b) (6)
	ERYTHEMA IN VACCINATION SITE	V59P17: (b) (6)
	ERYTHEMA INJECTION SITE	V59P17:
	ERYTHEMA RIGHT THIGH INJECTION SITE	V59P18:
	ERYTHEMA SITE INJECTION	V59P18:
	ERYTHEMA@INJECTION SITE	V59P13:
	INJECTION SITE ERYTHEMA	V59P13:
	INJECTION SITE REDNESS	V59P13: V59P13 (b) (6) V59P13 (b) (6)
	LOCAL REACTION ERYTHEMA AT INJECTION SITE	V59P18:
	REDNESS @ INJECTION SITE	V59P13: V59P13 (b) (6) V59P13 (b) (6)
	REDNESS ABOVE INJECTION SITE	V59P13:
	REDNESS AT INJECTION SITE	V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
	REDNESS AT INJECTION SITE LEFT DELTOID	V59P13:
	REDNESS BELOW INJECTION SITE	V59P13:
	REDNESS INJECTION SITE	V59P13:
INJECTION SITE HAEMORRHAGE	ECCHYMOSIS AT INJECTION SITE	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6)
		V59P17:
INJECTION SITE INDURATION	HARDNESS @ INJECTION SITE	V59P13: (b) (6)
	HARDNESS AT INJECTION	V59P13:
	HARDNESS AT INJECTION SITE	V59P13: V59P13 (b) (6) V59P13 (b) (6)
		V59P13:
	HARDNESS BELOW INJECTION SITE	V59P13:
	HARDNESS INJECTION SITE	V59P13:
	INDURATION @ INJECTION SITE	V59P13:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

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INJECTION SITE INDURATION	INDURATION AT INJECTION SITE	V59P17: (b) (6) V59P17: (b) (6) V59P17 (b) (6) V59P17: V59P6: (b) (6)
	INDURATION IN VACCINATION SITE	V59P17:
	INDURATION LEFT ARM AT INJECTION SITE	V59P18:
	INDURATION LOCAL REACTION AT INJECTION SITE	V59P18:
	INDURATION MENACWY SITE	V59P18:
	INDURATION RIGHT THIGH INJECTION SITE	V59P18:
	INDURATION TDAP SITE	V59P18:
	INDURATION-LOCAL REACTION (POST INJECTION SITE)	V59P18:
	INDURATION@ INJECTION SITE	V59P13:
	INJECTION SITE HARDNESS	V59P13: V59P13: (b) (6)
	INJECTION SITE INDURATION	V59P13: V59P13:
INJECTION SITE INFECTION	LOCAL INFECTION AT THE INJECTION SITE	V59P17 (b) (6)
INJECTION SITE IRRITATION	BURNING IN VACCINATION SITE.	V59P17 (b) (6)
INJECTION SITE MASS	SIX SMALL RAISED BUMPS AT INJECTION SITE	V59P13 (b) (6)
INJECTION SITE OEDEMA	EDEMA (LOCAL) AT INJECTION SITE	V59P17: (b) (6)
	EDEMA IN VACCINATION SITE	V59P17:
INJECTION SITE PAIN	INJECTION SITE PAIN	V59P13: (b) (6) V59P13: (b) (6) V59P13 (b) (6) V59P17: V59P17:
	LEFT ARM PAIN (VACCINATION SITE)	V59P17:
	LOCAL PAIN	V59P17: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17:
	LOCAL PAIN AT THE INJECTION SITE	V59P17:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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INJECTION SITE PAIN	LOCAL REACTOGENICITY: PAIN AT INJECTION SITE	V59P13: (b) (6)
	PAIN @ INJECTION SITE	V59P13:
	PAIN AT INJECTION SITE	V59P13: V59P13: (b) (6) V59P13 (b) (6)
		V59P13: V59P17:
	PAIN IN BACK OF INJECTION SITE ARM	V59P13:
	PAIN IN INJECTION SITE	V59P17:
	PAIN IN THE INJECTION SITE	V59P17: V59P17 (b) (6)
	PAIN IN VACCINATION SITE	V59P17:
	PAIN INJECTION SITE	V59P17: V59P17 (b) (6) V59P17 (b) (6)
		V59P17:
	PAIN LOCAL REACTION AT INJECTION SITE	V59P18:
	PAIN OF INJECTION SITE	V59P13:
	PAIN ON INJECTION SITE	V59P17:
	PAIN ON VACCINATION SITE	V59P17:
	TENDERNESS @ INJECTION SITE	V59P13:
	TENDERNESS ABOVE INJECTION SITE	V59P13:
INJECTION SITE PRURITUS	INJECTION SITE ITCHINESS	V59P13: (b) (6)
	INJECTION SITE ITCHING	V59P13:
	INJECTION SITE-ITCH	V59P13:
	INJECTION SITE-ITCHINESS	V59P13:
	ITCH @ INJECTION SITE	V59P13: V59P13: (b) (6)
	ITCHINESS AT INJECTION SITE	V59P13: V59P13:
	ITCHING @ INJECTION SITE	V59P13: V59P13:
	ITCHING AT INJECTION SITE	V59P13: V59P13: V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13:
	ITCHING AT VACCINATION SITE	V59P13: V59P13:
	ITCHING AT VACCINE SITE	V59P13:

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INJECTION SITE PRURITUS	ITCHNESS AT INJECTION SITE	V59P13: (b) (6)
	LEFT ARM PRURITUS (VACCINATION SITE)	V59P17:
	PRURITUS AT INJECTION SITE	V59P13: V59P13: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17:
	PRURITUS INJECTION SITE	V59P17: V59P17 (b) (6)
INJECTION SITE REACTION	DRY SKIN PATCH-LEFT ARM AT INJECTION SITE	V59P13: (b) (6)
	SHOULDER LEFT INDURATION AND ERYTHEMA (AT INJECTION SITE)	V59P17:
INJECTION SITE SWELLING	EXTENSIVE LIMB SWELLING LEFT ARM	V59P13 (b) (6)
	INJECTION SITE SMALL SWELLING	V59P13
	SWELLING @ INJECTION SITE	V59P13
	SWELLING AT INJECTION SITE	V59P13 V59P13 (b) (6)
	SWELLING LEFT DELTOID NOT ONLY IN THE INJECTION/ VACCINATION SITE	V59P11
	VACCINE SITE SWELLING	V59P13 (b) (6)
INJECTION SITE WARMTH	HOT TO TOUCH LEFT DELTOID AT INJECTION SITE	V59P13: (b) (6)
	INJECTION SITE WARM TO TOUCH	V59P13:
	INJECTION SITE-WARM TO TOUCH	V59P13:
	WARM INJECTION SITE	V59P17: V59P17 (b) (6)
	WARM TO TOUCH AT INJECTION SITE	V59P13:
	WARM TO TOUCH INJECTION SITE	V59P13:
	WARM VACCINATION SITE	V59P17:
	WARMTH @ INJECTION SITE	V59P13: V59P13: (b) (6)
	WARMTH AT INJECTION SITE	V59P13: V59P13:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
INJURY	CLOSED RIGHT KNEE TRAUMA	V59P17: (b) (6)
	CLOSED TRAUMA (LEFT ARM AND SHOULDER).	V59P17:
	CRANIOENCEPHALIC TRAUMA	V59P18:
	ELBOW TRAUMA RIGHT	V59P18:
	FINGER TRAUMA	V59P18:
	FINGERS LEFT HAND TRAUMA	V59P17:
	FOOT TRAUMA	V59P17: V59P18 (b) (6)
	GROIN INJURY	V59P13:
	HEAD TRAUMA/NECK STINGER	V59P13:
	LEFT COSTAL TRAUMA	V59P17:
	LEFT KNEE TRAUMA	V59P17:
	LEFT LEG HEMATOMA DUE TO TRAUMA	V59P17:
	LEG TRAUMATISM	V59P17:
	LUMBAGO DUE TO TRAUMA	V59P17:
	RIGHT HAND TRAUMA	V59P17:
	RIGHT LEG TRAUMATISM	V59P17:
	RIGHT WRIST TRAUMA	V59P6: (b) (6)
	SPINAL TRAUMA	V59P17: (b) (6)
	THIGH PAIN DUE TO TRAUMA	V59P17:
	TRAUMA	V59P18:
	TRAUMA 3RD DIGIT RIGHT HAND	V59P13:
	TRAUMA IN RIGHT KNEE	V59P17:
INSOMNIA	INSOMNIA	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P17:
		V59P17: V59P18: V59P6: (b) (6)
	SLEEPLESSNESS	V59P13:
INTENTIONAL OVERDOSE	NON LETHAL IBUPROFEN OVERDOSE	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
INTERVERTEBRAL DISC PROTRUSION	DISC HERNIATION	V59P17: (b) (6)
	HERNIATED C5-C6	V59P13:
	HERNIATED DISK	V59P17: V59P17 (b) (6)
	LUMBAR DISC HERNIATION	V59P17:
IRRITABILITY	IRRITABILITY	V59P13 (b) (6)
IRRITABLE BOWEL SYNDROME	IRRITABLE BOWEL	V59P13: (b) (6)
	IRRITABLE BOWEL SYNDROME	V59P13:
	IRRITABLE COLON	V59P17: V59P17 (b) (6) V59P17 (b) (6)
	IRRITABLE COLON EXACERBATION	V59P17:
JAW FRACTURE	FRACTURE LEFT MAXILLARY SINUS	V59P13 (b) (6)
JOINT DISLOCATION	ACROMION-CLAVICLE DISLOCATION	V59P17: (b) (6)
	CLOSED DISLOCATION RIGHT PATELLA	V59P6: (b) (6)
	DISLOCATED KNEE CAP R	V59P13: (b) (6)
	DISLOCATED LEFT SHOULDER	V59P13:
	PATELLAR SUBLUXATION	V59P13:
	TEMPOROMANDIBULAR JOINT LUXATION	V59P17:
JOINT HYPEREXTENSION	HYPEREXTENSION R THUMB	V59P13 (b) (6)
JOINT INJURY	HIP INJURY	V59P13: (b) (6) V59P13 (b) (6)
	INJURY TO HIP	V59P13:
	INJURY TO RIGHT ELBOW	V59P13:
	KNEE INJURY	V59P13:
	KNEE TRAUMA	V59P17: V59P18 (b) (6)
	LEFT WRIST INJURY	V59P13:
	R SHOULDER INJURY	V59P6: (b) (6)
	RIGHT ANKLE INJURY	V59P13: (b) (6)

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JOINT INJURY	RIGHT SHOULDER INJURY	V59P6: (b) (6)
	RT KNEE INJURY	V59P13: (b) (6)
	SHOULDER INJURY	V59P13:
JOINT SPRAIN	ANKLE SPRAIN	V59P13: (b) (6) V59P13 (b) (6) V59P17 (b) (6)
	FINGER SPRAINS	V59P13:
	KNEE SPRAIN	V59P13: V59P13 (b) (6)
	LEFT ANKLE SPRAIN	V59P6 (b) (6)
	LEFT FOOT SPRAIN	V59P17: (b) (6)
	LEFT LATERAL ANKLE SPRAIN	V59P6: (b) (6)
	LEFT WRIST SPRAIN	V59P6:
	R ANKLE SPRAIN	V59P13: (b) (6)
	RIGHT ANKLE SPRAIN	V59P13:
	RIGHT ANKLE'S SPRAIN	V59P11:
	RIGHT ARM SPRAIN	V59P18:
	RIGHT FOOT SPRAIN	V59P17:
	RIGHT KNEE SPRAIN	V59P6 (b) (6)
	RT. ANKLE SPRAIN	V59P13: (b) (6)
	SPRAIN L ANKLE	V59P13:
	SPRAIN OF LEFT ANKLE	V59P13:
	SPRAIN OF LEFT FOOT	V59P17:
	SPRAIN OF THUMB	V59P13:
	SPRAIN RIGHT THUMB	V59P13:
	SPRAINED ANKLE	V59P13:
	SPRAINED LEFT MIDDLE FINGER	V59P13:
	SPRAINED RIGHT ANKLE	V59P13:
	SPRAINED RIGHT INDEX FINGER	V59P13:
	TWISTED ANKLE	V59P13: V59P13: (b) (6)
	WRIST SPRAIN	V59P13: V59P6: (b) (6)

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JOINT STIFFNESS	IMMOBILE LEFT WRIST	V59P13: (b) (6)
	LEFT HIP STIFFNESS	V59P13:
JOINT SWELLING	RIGHT ANKLE-SWOLLEN	V59P13: (b) (6)
	SWELLING OF ANKLES	V59P13:
KIDNEY INFECTION	KIDNEY INFECTION	V59P13 (b) (6)
LACERATION	CHEST KNIFE WOUND	V59P17: (b) (6)
	LACERATION	V59P13:
LARYNGITIS	LARYNGITIS	V59P11 (b) (6) V59P13 (b) (6) V59P17 (b) (6)
LARYNGITIS ALLERGIC	ALLERGIC LARYNGITIS	V59P17 (b) (6)
LATENT TUBERCULOSIS	LATENT TUBERCULOSIS	V59P13 (b) (6)
LIGAMENT RUPTURE	ANTERIOR CRUCIATE LIGAMENT LACERATION	V59P13: (b) (6)
	RIGHT KNEE ANTERIOR CRUCIATE LIGAMENT TEAR	V59P13:
LIMB INJURY	FOOT INJURY	V59P13: (b) (6)
	INJURY RIGHT FOOT	V59P13:
	JAMMED FINGER RIGHT HAND	V59P6: (b) (6)
	JAMMED LEFT THUMB	V59P6:
	LEFT HAND INJURY	V59P13: (b) (6)
	LEFT MIDDLE FINGER INJURY	V59P13:
	PRETIBIAL (LEFT) INJURY	V59P18:
	RIGHT HAND INJURY	V59P13: V59P13 (b) (6)
	SOFT TISSUE LEFT THUMB INJURY	V59P13:
	TOE INJURY	V59P13: V59P6 (b) (6)
LIP OEDEMA	LIP EDEMA	V59P17 (b) (6)

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LIPOSUCTION	LIPOSUCTION	V59P17 (b) (6)
LIVER FUNCTION TEST ABNORMAL	ABNORMAL LIVER FUNCTION TEST	V59P13 (b) (6)
LOCALISED INFECTION	INFECTED GREAT TOE	V59P13: (b) (6)
	INFECTION OF RIGHT RING FINGER	V59P13:
LUMBAR SPINE FLATTENING	MILDLY STRAIGHTENING OF LUMBAR LORDOTIC CURVATURE	V59P13 (b) (6)
LYMPH GLAND INFECTION	INFECTED LYMPH NODES	V59P6 (b) (6)
LYMPH NODE PAIN	SORE LYMPH NODES UNDER LEFT ARM	V59P13 (b) (6)
LYMPHADENOPATHY	ADENOPATHY	V59P18: (b) (6)
	AXILLAR ADENOPATHY	V59P17: V59P17 (b) (6)
	AXILLARY ADENOPATHY	V59P17:
	AXILLARY ADENOPATHY LEFT	V59P17:
	AXILLARY LEFT LYMPHADENOPATHY	V59P17:
	CERVICAL LYMPHADENOPATHY	V59P13:
	INCREASE LEFT ARMPIT GLAND	V59P11:
	L AXILLA REACTIVE LYMPH NODE	V59P6: (b) (6)
	LEFT AXILLARY ADENOPATHY	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6)
		V59P17:
	LEFT CERVICAL ADENOPATHY	V59P17:
	LYMPHADENOPATHY	V59P13: V59P13 (b) (6)
	LYMPHADENOPATHY LEFT UNDERARM	V59P13:
	LYMPHADENOPATHY OF LATERAL CERVICAL OF LYMPHONODES	V59P11:
	PREAURICULAR ADENOPATHY	V59P17:
	SWOLLEN GLANDS	V59P13:
	SWOLLEN LYMPH NODE @ LEFT CLAVICLE	V59P13:
	SWOLLEN LYMPH NODE LEFT ARM	V59P13:

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LYMPHADENOPATHY	SWOLLEN LYMPH NODE LEFT AXILLARY	V59P13 (b) (6)
MAJOR DEPRESSION	MAJOR DEPRESSIVE DISORDER SEVERE WITH PSYCHOTIC FEATURES	V59P13 (b) (6)
MALAISE	GENERAL MALAISE MALAISE	V59P17: (b) (6) V59P11: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P11: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P13 (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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MALAISE	MALAISE	V59P18: (b) (6) V59P18: V59P18: V59P6 V59P6 V59P6 V59P18: (b) (6) V59P18: V59P18: V59P6: (b) (6) V59P6: V59P6: V59P18: (b) (6) V59P18: V59P6: (b) (6) V59P6: V59P6:
MALLORY-WEISS SYNDROME	MALLORY-WEISS SYNDROME	V59P17 (b) (6)
MASS	BUMP ON THE HEAD	V59P13 (b) (6)
MASTITIS	MASTITIS	V59P17 (b) (6)
MEDIAL TIBIAL STRESS SYNDROME	SHIN SPLINTS	V59P13 (b) (6)
MELAENA	BLACK TARRY STOOL	V59P13 (b) (6)
MELANOCYTIC NAEVUS	BENIGN NEVUS-RIGHT PREAURICULAR REMOVAL NEVUS	V59P13: (b) (6) V59P11:
MENINGITIS VIRAL	VIRAL MENINGITIS	V59P13 (b) (6)
MENISCUS LESION	BILATERAL LESION OF MENISCUS MENISCUS TEAR	V59P17 (b) (6) V59P13
MENOPAUSAL DEPRESSION	PREMENSTRUAL EXACERBATION OF DEPRESSION	V59P13 (b) (6)
MENOPAUSAL SYMPTOMS	PERIMENOPAUSAL BLEEDING	V59P13 (b) (6)
MENORRHAGIA	HYPERMENORRHEA	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
METABOLIC ACIDOSIS	METABOLIC ACIDOSIS	V59P13 (b) (6)
METABOLIC SYNDROME	METABOLIC SYNDROME	V59P13 (b) (6)
MIGRAINE	ABDOMINAL MIGRAINE EXACERBATION	V59P13: (b) (6)
	MIGRAINE	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P17: V59P17: V59P17: V59P18: V59P18:
	MIGRAINE COMMON W/O INTRACTABLE	V59P13:
	MIGRAINE CRISIS	V59P17:
	MIGRAINE EXACERBATION	V59P17: V59P17 (b) (6) V59P17 (b) (6)
	MIGRAINE FREQUENCY INCREASE	V59P13:
	MIGRAINE HEADACHE	V59P13: V59P13: (b) (6)
	MIGRAINE HEADACHES	V59P13: V59P6 (b) (6)
MITRAL VALVE PROLAPSE	BORDERLINE MITRAL VALVE PROLAPSE	V59P13 (b) (6)
MOLLUSCUM CONTAGIOSUM	MOLLUSCUM CONTAGIOSUM	V59P13 (b) (6)
MORTON'S NEUROMA	L FOOT MORTON'S NEUROMA	V59P13 (b) (6)
MOTION SICKNESS	CAR SICKNESS	V59P11: (b) (6)
	SEA SICKNESS	V59P17:
MOUTH INJURY	LIP INJURY	V59P13 (b) (6)
MULTIPLE ALLERGIES	ALLERGIES	V59P13 (b) (6)
MULTIPLE DRUG OVERDOSE INTENTIONAL	INTENTIONAL INGESTION OF MULTIPLE MEDICATIONS	V59P13 (b) (6)
MULTIPLE INJURIES	POLYTRAUMATISM	V59P17 (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
MUSCLE CONTRACTIONS INVOLUNTARY	FASCICULATIONS AT RIGHT CHEEK	V59P17: (b) (6)
	MUSCULAR CONTRACTION	V59P18:
MUSCLE CONTRACTURE	CERVICAL CONTRACTURE	V59P17 (b) (6)
MUSCLE SPASMS	BACK CRAMPS	V59P13: (b) (6)
	CERVICAL SPASM	V59P17:
	CRAMP	V59P17:
	CRAMPING	V59P13:
	CRAMPING OF FEET	V59P13:
	CRAMPS	V59P13: V59P13 (b) (6)
	CRAMPS RIGHT LEG	V59P17:
	LEFT ARM SPASM	V59P17:
	LEFT HAND SPASM	V59P13:
	LEFT NECK SPASM	V59P13:
	LEG CRAMP	V59P13:
	LEG PAIN-UPPER, POSTERIOR; CRAMPING LIKE	V59P13:
	MUSCLE SPASM (TRAPEZIUS AND RHOMBOID)	V59P17:
	MUSCLE SPASM LOWER BACK	V59P13:
	MUSCLE SPASMS	V59P13:
	MUSCULAR SPASM RIGHT ARM.	V59P17:
MUSCLE STRAIN	ADDUCTOR TEAR	V59P17: (b) (6)
	GROIN PULL	V59P13:
	MUSCLE STRAIN RIGHT ARM	V59P13:
	PULLED BACK MUSCLE PAIN	V59P13:
	PULLED MUSCLE LEFT UPPER ARM	V59P13:
	PULLED RIGHT QUADRICEP MUSCLE	V59P13:
MUSCULAR WEAKNESS	VACCINATED ARM FEELS WEAK FROM SHOULDER TO ELBOW	V59P6: (b) (6)
	WEAKNESS IN ARMS	V59P13: (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
MUSCULAR WEAKNESS	WEAKNESS OF THE ARM	V59P17 (b) (6)
MUSCULOSKELETAL CHEST PAIN	CHEST WALL PAIN	V59P13 (b) (6) V59P13 (b) (6)
MUSCULOSKELETAL DISORDER	SOMATIC DYSFUNCTION OF UPPER EXTREMITIES/PELVIS	V59P13 (b) (6)
MUSCULOSKELETAL PAIN	BILATERAL SHOULDER PAIN	V59P13: (b) (6)
	BLOOD RHEUMATISM	V59P11:
	BOTH ARMS MYALGIA AND ARTHRALGIA	V59P13:
	L SHOULDER PAIN	V59P13:
	LEFT SHOULDER PAIN	V59P13: V59P6: (b) (6)
	MUSCULOSKELETAL PAIN	V59P13: V59P13: (b) (6)
	PERSISTENT SHOULDER PAIN	V59P13:
	SHOULDER PAIN	V59P13:
	SHOULDERS PAIN	V59P17:
	SORE SHOULDER	V59P13:
MUSCULOSKELETAL STIFFNESS	MUSCLE STIFFNESS IN NECK	V59P13: (b) (6)
	STIFF NECK	V59P13:
	STIFFNESS-LOWER BACK	V59P13:
MYALGIA	LEFT ARM MUSCULAR PAIN	V59P17: (b) (6)
	MUSCLE ACHES: ARMS AND CALVES	V59P13:
	MYALGIA	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P13: V59P13: (b) (6)
		V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:

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MYALGIA	MYALGIA	V59P13: (b) (6) V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P6: (b) (6)
		V59P13: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P6 (b) (6)
		V59P13: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P6: (b) (6)
	MYALGIA AT LOWER LIMBS	V59P17: (b) (6)
	MYALGIA IN THE LEFT ARM	V59P17:
	MYALGIAS	V59P17:
	SORE MUSCLES FROM WORKING OUT	V59P13:
MYASTHENIA GRAVIS	MYASTHENIA GRAVIS	V59P13 (b) (6)
MYCOPLASMA INFECTION	MYCOPLASMA	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)
MYOCLONIC EPILEPSY	JUVENILE MYOCLONIC EPILEPSY	V59P13 (b) (6)
NAIL BED INFECTION	INFECTED LEFT GREAT TOENAIL	V59P6: (b) (6)
	INFECTION OF THUMBNAIL-BED	V59P13: (b) (6)
	L GREAT TOENAIL INFECTION	V59P13:
NAIL OPERATION	NAIL EXTRACTION	V59P18 (b) (6)

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NASAL CONGESTION	NASAL CONGESTION	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6)
	NASAL CONGESTION "STUFFY NOSE"	V59P13:
	RUNNING/STUFFY NOSE	V59P13:
	STUFFY NOSE	V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P6: (b) (6)
NASAL DRYNESS	DRY SINUSES	V59P13 (b) (6)
NASOPHARYNGITIS	ACUTE RHINOPHARYNGITIS	V59P17: (b) (6) V59P17 (b) (6)
	CATARRH	V59P17:
	COLD	V59P11: V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P13: V59P13: (b) (6) V59P17: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:
	COLD SYMPTOMS	V59P11: V59P11: (b) (6) V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6)
	COLD VIRUS	V59P13: (b) (6)
	COLD.	V59P17:
	COMMON COLD	V59P11: V59P11 (b) (6) V59P11 (b) (6)

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NASOPHARYNGITIS	COMMON COLD	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P11: V59P13: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P17: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:
	EXCERBATION OF COLD SYMPTOMS	V59P13:
	HEAD COLD	V59P13: V59P13 (b) (6) V59P6 (b) (6) V59P6: (b) (6)
	RHINOPHARYNGITIS	V59P17: (b) (6) V59P17 (b) (6)
	SINUS COLD	V59P13:
	SPRING CATARRH	V59P11:
	UPPER AIRWAY CATARRH	V59P17: V59P17 (b) (6)
NAUSEA	NAUSEA	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P11: V59P11: V59P11: V59P13: V59P13: (b) (6) V59P13: V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
NAUSEA	NAUSEA	V59P17: (b) (6) V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: V59P17: (b) (6) V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: V59P17: (b) (6) V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6:
NECK CRUSHING	NECK TRAUMA	V59P18 (b) (6)
NECK INJURY	CERVICAL NECK STRAIN CERVICAL SPRAIN NECK SPRAIN NECK STRAIN	V59P6: (b) (6) V59P13: (b) (6) V59P6: (b) (6) V59P13: (b) (6)
NECK PAIN	ACHE IN BACK OF NECK CERVICAL PAIN CERVICALGIA NECK PAIN	V59P6: (b) (6) V59P17: (b) (6) V59P17: V59P11: V59P13: V59P13: V59P13: V59P17: V59P13: (b) (6) V59P13: V59P13: V59P18: V59P13: (b) (6) V59P13: V59P17: V59P6: (b) (6)
NEPHRECTOMY	NEPHRECTOMY	V59P17 (b) (6)
NEPHROLITHIASIS	KIDNEY STONE	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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NEPHROLITHIASIS	KIDNEY STONE (LEFT SIDE) RENAL CALCULI RENAL CALCULOSIS	V59P13: (b) (6) V59P13: V59P11:
NEURALGIA	OCCIPITAL NEURALGIA	V59P13 (b) (6)
OBESITY	OBESITY	V59P18 (b) (6)
OCULAR HYPERAEMIA	RED EYES	V59P13 (b) (6)
ODYNOPHAGIA	ODYNOPHAGIA	V59P17: (b) (6) V59P17: (b) (6) V59P17 (b) (6) V59P18: V59P18:
OEDEMA PERIPHERAL	EDEMA IN RIGHT FOOT LEFT ARM SWELLING SWOLLEN RIGHT ARM	V59P17: (b) (6) V59P13: V59P13:
OLIGOMENORRHOEA	MENSTRUAL PERIOD PROLONGED BY 5 DAYS SECONDARY OLIGOMENORRHEA	V59P13: (b) (6) V59P6: (b) (6)
OMPHALITIS	PERIUMBILICAL SKIN INFECTION	V59P17 (b) (6)
ONYCHOGRYPHOSIS	ONYCHOGRYPHOSIS	V59P18 (b) (6)
ONYCHOMYCOSIS	HAND NAILS MYCOSIS	V59P17 (b) (6)
OPEN WOUND	LIP LACERATION	V59P6 (b) (6)
ORAL DISORDER	LESIONS AROUND MOUTH	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ORAL HERPES	EXACERBATION OF HERPETIFORM APHTHOUS STOMATITIS	V59P13: (b) (6)
	HERPES (COLD SORE)	V59P6: (b) (6)
	HERPES LABIALIS	V59P17: (b) (6)
	HERPES SIMPLEX LABIAL	V59P17:
	HERPES-COLD SORE	V59P6: (b) (6)
	HSV INFECTION (ORAL)	V59P6:
	LABIAL HERPES	V59P17: (b) (6) V59P17 (b) (6)
	LABIAL HERPES SIMPLEX	V59P17:
	ORAL HERPES	V59P17: V59P17 (b) (6)
	ORAL HERPES SIMPLEX	V59P13:
ORAL PAIN	MOUTH PAIN	V59P13: (b) (6)
	SORE MOUTH	V59P13:
	SORE MOUTH AFTER GETTING BRACES ADJUSTED	V59P13:
OSTEOARTHRITIS	ARTHROSIS IN KNEES	V59P17: (b) (6)
	HIP ARTHROSIS	V59P17:
	KNEES ARTHROSIS	V59P17:
	LEFT KNEE ARTHROSIS	V59P17:
OSTEOCHONDROSIS	OSGOOD SCHLATTER	V59P13: (b) (6)
	OSGOOD SCHLATTER'S	V59P13:
	OSTEOCHONDRITIS	V59P17: V59P18 (b) (6)
OTITIS EXTERNA	ACUTE OTITIS EXTERNAL RIGHT EAR	V59P6: (b) (6)
	OTITIS EXTERNA	V59P13: (b) (6) V59P13 (b) (6) V59P17 (b) (6)
	SWIMMER'S EAR	V59P13:
OTITIS MEDIA	LEFT OTITIS MEDIA	V59P13: (b) (6)
	MIDDLE EAR INFECTION	V59P13:
	OTITIS MEDIA	V59P13: V59P13 (b) (6) V59P13 (b) (6)

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OTITIS MEDIA	OTITIS MEDIA	V59P13: (b) (6) V59P13: (b) (6) V59P13 (b) (6) V59P17: V59P6: (b) (6)
	OTITIS SUPPURATIVE	V59P11:
	RIGHT SEROUS OTITIS MEDIA	V59P13:
OTITIS MEDIA ACUTE	ACUTE OTITIS MEDIA	V59P18 (b) (6) V59P18 (b) (6)
OVARIAN CYST	CYST ON OVARY	V59P13: (b) (6)
	CYST OVARIAN (LEFT)	V59P17:
	RIGHT OVARIAN CYST	V59P17:
OVERDOSE	DRUG OVERDOSE	V59P13 (b) (6)
OVULATION PAIN	MID PAIN	V59P11 (b) (6)
PAIN	BODY ACHE	V59P13: (b) (6)
	BODY SORENESS	V59P13:
	PAIN	V59P17: V59P17: (b) (6) V59P18: (b) (6)
		V59P18: V59P18: V59P18:
		V59P18: V59P18: V59P18:
		V59P18: V59P18:
	PAIN RIGHT SIDE OF BODY	V59P13:
	PAIN UNDER LEFT ARM	V59P13:
	RIGHT ARM PAIN, PAIN IN LEGS AND KNEES	V59P17:
	SORENESS FROM EXERCISE	V59P13:
PAIN IN EXTREMITY	ARM PAIN	V59P13: (b) (6) V59P18 (b) (6)
	ARM PAIN-LEFT	V59P13:
	BILATERAL ARM PAIN	V59P17:

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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PAIN IN EXTREMITY	CALF MUSCLE PAIN	V59P13: (b) (6)
	FOOT ACHE	V59P13:
	FOOT PAIN	V59P13:
	FOOT PAIN - ETIOLOGY UNKNOWN	V59P13:
	FOOT PAIN-RIGHT	V59P13:
	HEEL PAIN	V59P13: V59P13: (b) (6) V59P17: V59P17: (b) (6)
	LEFT ARM PAIN	V59P13: V59P17:
	LEFT FOOT PAIN	V59P17:
	LEFT HEEL PAIN	V59P17:
	LEFT LEG PAIN	V59P17:
	LEFT UPPER ARM PAIN	V59P17: V59P17 (b) (6)
	LEG ACHE DUE TO EXERCISE	V59P13:
	LEG MUSCLE PAIN	V59P13:
	LEG PAIN	V59P13:
	LEG PAIN (LEFT LEG)	V59P17:
	LEG PAIN-RIGHT	V59P13:
	LEGS PAIN	V59P17:
	PAIN (L) ARM	V59P13:
	PAIN IN ARM	V59P13:
	PAIN IN LEFT ARM	V59P13:
	PAIN IN LEGS	V59P18:
	PAIN IN RIGHT ARM	V59P17:
	PAIN IN RIGHT FOOT	V59P17:
	PAIN IN RIGHT LEG	V59P17:
	PAIN IN RIGHT THIGH	V59P13:
	PAIN LEFT LEG	V59P13:
	PAIN RIGHT ARM	V59P13:
	PAIN RIGHT THIGH	V59P18:
	PAIN-LEFT ARM ABDUCTION	V59P13:

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PAIN IN EXTREMITY	R LEG PAIN	V59P6: (b) (6)
	RIGHT ARM PAIN	V59P13: (b) (6) V59P17 (b) (6)
	RIGHT FOOT PAIN	V59P13:
	RIGHT HEEL PAIN.	V59P17:
	RIGHT LEG PAIN	V59P17:
	RIGHT THIGH PAIN	V59P13:
	SHARP PAINS IN UPPER LEFT ARM	V59P6: (b) (6)
	SORENESS IN LEFT ARM AND LEG	V59P6:
PAIN IN JAW	JAW PAIN	V59P13 (b) (6)
PALPITATIONS	PALPITATIONS	V59P13: (b) (6) V59P17 (b) (6)
	PALPITATIONS WITH EXERCISING	V59P13:
PANNICULITIS	PANNICULITIS	V59P13 (b) (6)
PAPILLOMA	BENIGN GALACTOPHOROUS DUCTS PAPILLOMATOSIS	V59P17 (b) (6)
PARAESTHESIA	3RD/4TH FINGER PARESTHESIA	V59P13: (b) (6)
	HANDS PARESTHESIA	V59P17:
	LEFT HAND PARESTHESIA	V59P17:
	LEFT LEG TINGLING	V59P17:
	PARESTHESIA HANDS	V59P17:
	PARESTHESIA IN RIGHT ARM	V59P17:
	PARESTHESIA OF LEFT ARM	V59P17:
	PARESTHESIAS	V59P17:
	PARESTHESIAS AT RIGHT ARM	V59P17:
	PARESTHESIAS AT THE FIRST FINGER OF BOTH HANDS	V59P17:
	RIGHT CHEST PARESTHESIA	V59P17:

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Table 93

Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
PARAESTHESIA	TINGLING (LEFT HAND)	V59P11 (b) (6)
PARANASAL SINUS HYPERSECRETION	SINUS DRAINAGE	V59P13 (b) (6) V59P13 (b) (6) V59P13 (b) (6)
PARASITIC GASTROENTERITIS	INTESTINAL PARASITISM	V59P17 (b) (6)
PARONYCHIA	EARLY PARONYCHIA ONYCHIA RING FINGER RIGHT HAND PARONYCHIA RING FINGER RIGHT HAND	V59P13: (b) (6) V59P13: V59P13:
PELVIC FRACTURE	PELVIS FRACTURE	V59P6 (b) (6)
PELVIC INFLAMMATORY DISEASE	INFLAMMATORY PELVIC DISEASE PELVIC INFLAMATORY DISEASE (PID) PELVIC INFLAMMATORY DISEASE	V59P17: (b) (6) V59P17: V59P13:
PERIODONTAL OPERATION	PERIODONTAL SURGERY	V59P6 (b) (6)
PERIORBITAL CELLULITIS	PERIORBITAL CELLULITIS	V59P13 (b) (6)
PERITONSILLAR ABSCESS	PERITONSILLAR ABSCESS	V59P13 (b) (6) V59P13 (b) (6)
PERTUSSIS	PERTUSSIS	V59P13 (b) (6)
PETECHIAE	PETECHIA (NECK AREA)	V59P13 (b) (6)
PETIT MAL EPILEPSY	SEIZURE, PETIT MAL	V59P13 (b) (6)
PHARYNGEAL OEDEMA	THROAT CONGESTION	V59P13 (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
PHARYNGITIS	ACUTE PHARYNGITIS ERYTHEMATOUS PHARYNGITIS PHARYNGITIS	V59P13: (b) (6) V59P13 (b) (6) V59P17 (b) (6) V59P17: V59P11: V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P13: V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: V59P6: V59P6: V59P6:
	THROAT INFECTION	V59P18: (b) (6) V59P18 (b) (6) V59P18 (b) (6) V59P18:
PHARYNGITIS BACTERIAL	BACTERIAL PHARYNGITIS	V59P17 (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers		
PHARYNGITIS STREPTOCOCCAL	STREP PHARYNGITIS	V59P13: (b) (6)	V59P13 (b) (6)	V59P13 (b) (6)
		V59P6: (b) (6)		
	STREP THROAT	V59P13: (b) (6)	V59P13: (b) (6)	V59P13: (b) (6)
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P6: (b) (6)	V59P6: (b) (6)	
PHARYNGOLARYNGEAL PAIN	SORE THROAT	V59P11: (b) (6)	V59P11: (b) (6)	V59P11: (b) (6)
		V59P11:	V59P11:	V59P11:
		V59P13:	V59P13: (b) (6)	V59P13: (b) (6)
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P17:	V59P17:
		V59P17:	V59P17:	V59P18:
		V59P6: (b) (6)	V59P6: (b) (6)	V59P6: (b) (6)
		V59P6:	V59P6:	V59P6:
		V59P6:	V59P6:	V59P6:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
PHARYNGOLARYNGEAL PAIN	SORE THROAT SORE THROAT LEFT SIDE OF THROAT THROAT PAIN	V59P6: (b) (6) V59P13: (b) (6) V59P11: V59P18: V59P17: (b) (6) V59P18: (b) (6) V59P18: (b) (6) V59P18: (b) (6)
PHARYNGOTONSILLITIS	PHARYNGOTONSILLITIS	V59P18 (b) (6) V59P18 (b) (6)
PHLEBITIS	PHLEBITIS	V59P13 (b) (6)
PILONIDAL CYST	PILONIDAL CYST	V59P13 (b) (6)
PITUITARY TUMOUR BENIGN	HYPOPHYSEAL MICROADENOMA	V59P18 (b) (6)
PITYRIASIS ROSEA	PITYRIASIS ROSEA	V59P13 (b) (6)
PLANTAR FASCIITIS	PLANTAR FASCIITIS	V59P13 (b) (6)
PNEUMONIA	PNEUMONIA PNEUMONIAE	V59P13: (b) (6) V59P13: V59P13: V59P17: V59P13: V59P13: (b) (6) V59P13: V59P13: V59P17: V59P13: (b) (6) V59P13: V59P13: V59P17:
PNEUMONIA PRIMARY ATYPICAL	EARLY ATYPICAL PNEUMONIA POSSIBLE ATYPICAL PNEUMONIA	V59P6: (b) (6) V59P6:
POLYCYTHAEMIA VERA	ERYTHEMIA	V59P17 (b) (6)
POST HERPETIC NEURALGIA	POST HERPETIC NEURALGIA	V59P17 (b) (6)
POST-TRAUMATIC STRESS DISORDER	POST TRAUMATIC STRESS SYNDROME	V59P13 (b) (6)

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
POSTMENOPAUSAL HAEMORRHAGE	POST-MENOPAUSAL BLEEDING	V59P13 (b) (6)
POSTOPERATIVE WOUND INFECTION	SURGICAL SITE INFECTION	V59P17 (b) (6)
POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME	POSITIONAL ORTHOSTATIC TACHYCARDIA SYNDROME	V59P13 (b) (6)
PREMENSTRUAL SYNDROME	PMS PRE-MENSTRUAL SYNDROME	V59P13 (b) (6)
PROCEDURAL PAIN	MOUTH ACHE RELATED TO BRACES	V59P13: (b) (6)
	MOUTH PAIN FROM BRACES	V59P13:
	PAIN DUE TO SURGICAL REMOVAL OF CERVICAL DYSPLASIA	V59P13:
	PAIN FROM VASECTOMY	V59P13:
	PAIN-WISDOM TEETH EXTRACTION	V59P13:
	WISDOM TEETH PULLED-PAIN	V59P13:
PRURIGO	PRURIGO AT HIP, THIGHS, ARMS AND FINGERS (BOTH HANDS)	V59P17 (b) (6)
PRURITUS	ITCH	V59P13: (b) (6)
	ITCHING	V59P13:
	PRURITUS	V59P13: V59P17 (b) (6) V59P17 (b) (6)
	PRURITUS IN RIGHT FOOT	V59P17:
PRURITUS GENERALISED	GENERALIZED PRURITUS	V59P17 (b) (6)
PSORIASIS	PSORIASIS	V59P13 (b) (6)
PTERYGIUM	PTERYGIUM IN RIGHT EYE	V59P17 (b) (6)
PULMONARY CONGESTION	CHEST CONGESTION	V59P13: (b) (6) V59P13: (b) (6) V59P13 (b) (6)
		V59P13: V59P13:
PULMONARY EMBOLISM	PULMONARY EMBOLI	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
PYODERMA	PYODERMATITIS	V59P18 (b) (6)
PYREXIA	FEVER	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P13: V59P13: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P18: V59P6: (b) (6) V59P6: (b) (6)
RADIUS FRACTURE	CLOSED DISTAL RADIUS FRACTURE	V59P13: (b) (6)
	LEFT RADIUS FRACTURE	V59P11:
	RIGHT RADIAL FRACTURE	V59P6: (b) (6)
	RIGHT RADIUS FRACTURE	V59P18: (b) (6)
RASH	EXANTHEMA	V59P17: (b) (6)
	FACE RASH	V59P13:
	RASH	V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
...Continued from previous page		
RASH	RASH	V59P18: (b) (6) V59P18 (b) (6)
	RASH BEHIND RIGHT KNEE	V59P13:
	RASH INNER ASPECT L ARM	V59P13:
	RASH ON ABDOMEN & BACK	V59P13:
	RASH ON FEET + ANKLES	V59P13:
	RASH ON LEFT ARM	V59P13:
	RASH ON LEFT UPPER ABDOMEN	V59P13:
	RASH ON TRUNK AND EXTREMITIES	V59P6: (b) (6)
RASH MACULAR	MACULE	V59P17 (b) (6)
RASH PRURITIC	PRURIGINOUS EXHANTEMA	V59P11 (b) (6) V59P11 (b) (6)
RECTAL HAEMORRHAGE	RECTAL BLEEDING	V59P13 (b) (6)
RENAL COLIC	RENAL COLIC	V59P17 (b) (6)
RESPIRATORY DISORDER	UPPER RESPIRATORY ILLNESS	V59P13 (b) (6)
RESPIRATORY FAILURE	RESPIRATORY FAILURE	V59P13 (b) (6)
RESPIRATORY TRACT INFECTION	RESPIRATORY TRACT INFECTION	V59P17 (b) (6) V59P18 (b) (6)
RESPIRATORY TRACT INFECTION VIRAL	RESPIRATORY VIRUS	V59P13 (b) (6)
RESTLESSNESS	RESTLESS	V59P13 (b) (6)
RETINAL DETACHMENT	RETINAL DETACHMENT	V59P17 (b) (6)
RHABDOMYOLYSIS	RHABDOMYOLYSIS	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
RHINITIS	ACUTE RHINITIS	V59P11: (b) (6) V59P17 (b) (6)
	EXACERBATION RHINITIS	V59P17:
	RHINITIS	V59P11: V59P11: (b) (6) V59P11: (b) (6)
		V59P11: V59P11: V59P17:
		V59P17: V59P17: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P18:
		V59P18: V59P18:
RHINITIS ALLERGIC	ALLERGIC RHINITIS	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
		V59P17: V59P17: V59P17:
		V59P17: V59P17: V59P17:
		V59P17: V59P17:
	ALLERGIC RHINTIS CRISIS	V59P17:
	ALLERGY (RHINITIS)	V59P18:
	EXACERBATION OF ALLERGIC RHINITIS	V59P17:
	RHINITIS (ALLERGIC)	V59P18:
	RHINITIS ALLERGIC	V59P11:
RHINITIS SEASONAL	SEASONAL ALLERGIC RHINITIS	V59P13 (b) (6)
RHINORRHOEA	RHINORRHEA	V59P13: (b) (6) V59P17: (b) (6)
	RUNNY NOSE	V59P13: V59P13: V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P13:
	SNEEZY RUNNY NOSE	V59P13:
RHONCHI	RHONCHUS IN LEFT LUNG	V59P18 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
ROAD TRAFFIC ACCIDENT	ALL TERRAIN VEHICULAR ACCIDENT WITH TRAUMA	V59P13: (b) (6)
	BODY SORENESS FROM AUTOMOBILE ACCIDENT	V59P13:
	LEG TRAUMA POST MOTOR VEHICLE ACCIDENT	V59P13:
	SHOULDER PAIN (AUTO ACCIDENT)	V59P13:
	TRAUMA DUE TO MOTOR VEHICLE ACCIDENT	V59P13:
ROTATOR CUFF REPAIR	ROTATOR CUP SURGERY	V59P13 (b) (6)
ROTATOR CUFF SYNDROME	IMPINGEMENT SHOULDER SYNDROME	V59P13: (b) (6)
	ROTATOR CUFF TENDONITIS	V59P13:
SCIATICA	SCIATALGY	V59P17: (b) (6)
	SCIATIC NEURALGIA	V59P17:
	SCIATICA	V59P13:
SEASONAL ALLERGY	HAY FEVER	V59P11: (b) (6) V59P6: (b) (6)
	SEASONAL ALLERGIES	V59P13: V59P13: (b) (6)
SELECTIVE IGM IMMUNODEFICIENCY	IGM DEFICIENCY	V59P6 (b) (6)
SEPTOPLASTY	SEPTOPLASTY	V59P17 (b) (6)
SIALOADENITIS	SALIVARY GLAND INFECTION	V59P6 (b) (6)
SIMPLE PARTIAL SEIZURES	SIMPLE PARTIAL SEIZURE	V59P13 (b) (6)
SINUS CONGESTION	CONGESTED SINUSES	V59P13: (b) (6)
	SINUS CONGESTION	V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P13: V59P13: V59P6: (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
SINUS HEADACHE	SINUS HEADACHE	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13:
	SINUS PAIN	V59P13:
	SINUS PRESSURE	V59P13:
SINUSITIS	RHINOSINUSITIS	V59P11: (b) (6)
	SINUS INFECTION	V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P6: (b) (6) V59P6 (b) (6)
	SINUSITIS	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P18: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6)
SKIN DISCOLOURATION	LOCALIZED SKIN DISCOLORATION	V59P13: (b) (6)
	PURPLE SPOTS RT FRONT THIGH	V59P13:
SKIN INFECTION	INFECTION (CUTANEOUS) (FOOT FINGER)	V59P18 (b) (6)
SKIN LACERATION	FINGER LACERATION	V59P13: (b) (6)
	LACERATION LEFT HAND	V59P13:
	LACERATION R THUMB	V59P13:
	LACERATION RIGHT MIDDLE FINGER	V59P13:
	LACERATION RIGHT THUMB	V59P13:

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SKIN LACERATION	LACERATION TO LEFT RING FINGER	V59P13: (b) (6)
	LACERATION-FINGER	V59P13:
	LACERATION-R ARM	V59P13:
	RIGHT 4TH DISTAL PHALANX LACERATION	V59P13:
	RIGHT ELBOW LACERATION	V59P13:
	RIGHT INDEX FINGER LACERATION	V59P13:
	SUPERFICIAL LACERATION TO LEFT FOREHEAD AND NOSE	V59P6: (b) (6)
SKIN NODULE	SMALL PURPLE NODULE SKIN	V59P13 (b) (6)
SKIN PAPILLOMA	WART ON LT FOREHEAD	V59P13 (b) (6)
SNEEZING	SNEEZING	V59P13 (b) (6)
SNORING	SNORING-EXACERBATION	V59P13 (b) (6)
SOFT TISSUE INJURY	SOFT TISSUES TRAUMA	V59P17 (b) (6)
SOMNOLENCE	DROWSINESS	V59P17: (b) (6)
	DROWSINESS.	V59P17:
	SLEEPINESS	V59P11: V59P11: (b) (6) V59P17: (b) (6)
		V59P17: V59P17: (b) (6) V59P17: (b) (6)
		V59P17:
	SOMNOLENCE	V59P13: V59P17 (b) (6)
SPINAL COMPRESSION FRACTURE	T5 COMPRESSION FRACTURE	V59P13 (b) (6)
SPINAL DEFORMITY	CERVICAL RECTIFICATION	V59P17 (b) (6)
SPLENOMEGALY	SPLENOMEGALY	V59P13 (b) (6) V59P6 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
SPLINTER	R THUMB SPLINTER	V59P13 (b) (6)
SPORTS INJURY	SOCCER INJURY TO LEFT ANKLE	V59P6 (b) (6)
STAPHYLOCOCCAL INFECTION	METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS	V59P13: (b) (6)
	RIGHT LEG ABCESS WITH METHICILLIN RESISTANT STAPH AUREUS	V59P13:
	STAPH INFECTION	V59P13 (b) (6) V59P13 (b) (6)
STOMACH DISCOMFORT	UPSET STOMACH	V59P13: (b) (6) V59P13: (b) (6) V59P13 (b) (6) V59P13: V59P6: (b) (6)
STOMATITIS	MOUTH SORES	V59P13: (b) (6)
	SORE ON ROOF OF MOUTH	V59P13:
	STOMATITIS	V59P11:
STRESS	STRESS	V59P18 (b) (6) V59P18 (b) (6)
STRESS FRACTURE	STRESS FRACTURE RIGHT FEMUR	V59P6 (b) (6)
SUBCUTANEOUS ABSCESS	FACE ABSCESS	V59P17: (b) (6)
	GLUTEAL ABSCESS	V59P17:
	LEFT AXILLARY ABSCESS	V59P17:
	RIGHT EAR ABSCESS	V59P17:
	SKIN ABSCESS	V59P17:
SUICIDAL IDEATION	SUICIDE IDEATION	V59P13 (b) (6)
SUICIDE ATTEMPT	SUICIDE ATTEMPT	V59P13 (b) (6) V59P13 (b) (6)
SUNBURN	SUNBURN	V59P13 (b) (6) V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
SYNCOPE	FAINTING SPELL	V59P6: (b) (6)
	LIPOTHYMIA	V59P17: (b) (6)
	NEW SYNCOPAL EPISODE	V59P13:
	SYNCOPAL EPISODE	V59P13:
	SYNCOPAL EVENT	V59P13:
	SYNCOPE	V59P13: V59P13: (b) (6) V59P13: (b) (6)
		V59P13: V59P13: V59P13:
		V59P17: V59P17:
SYNCOPE VASOVAGAL	POST-VACCINATION VASO-VAGAL REACTION	V59P13: (b) (6)
	SYNCOPAL EPISODE DURING BLOOD DRAW	V59P13:
	VASOVAGAL EPISODE	V59P13:
	VASOVAGAL SYNCOPE	V59P13: V59P13 (b) (6) V59P17 (b) (6)
		V59P6: (b) (6)
SYNOVIAL CYST	AXILLARY GANGLION	V59P17 (b) (6)
SYPHILIS	LUES (SYPHILIS)	V59P17 (b) (6)
TACHYCARDIA	TACHYCARDIA	V59P17 (b) (6) V59P17 (b) (6) V59P17 (b) (6)
TEMPERATURE INTOLERANCE	OVERHEATED	V59P13 (b) (6)
TEMPOROMANDIBULAR JOINT SYNDROME	TEMPOROMANDIBULAR JOINT DYSFUNCTION	V59P13 (b) (6)
TENDERNESS	TENDERNESS IN GLANDS OF THROAT	V59P13: (b) (6)
	TENDERNESS TO RIGHT ANTERIOR CERVICAL AREA	V59P6: (b) (6)
TENDONITIS	BILATERAL ACHILLES TENDONITIS	V59P13: (b) (6)
	BILATERAL TENDONITIS-ANKLES	V59P13:
	LEFT ARM TENDINITIS	V59P17:

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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TENDONITIS	PATELLAR TENDONITIS TENDINITIS	V59P13: (b) (6) V59P17:
TENSION HEADACHE	TENSION HEADACHE TENSIONAL HEADACHE	V59P13: (b) (6) V59P17 (b) (6) V59P17:
TESTICULAR TORSION	LEFT TESTICULAR TORSION	V59P11 (b) (6)
THERAPEUTIC AGENT TOXICITY	SALICYLATE TOXICITY	V59P13 (b) (6)
THERMAL BURN	BURN LEFT ARM BURN ON HAND	V59P13: (b) (6) V59P13:
THIRST	EXCESSIVE THIRST THIRST	V59P13: (b) (6) V59P17:
THROAT IRRITATION	ITCHY THROAT THROAT PRURITUS	V59P13: (b) (6) V59P17:
TIBIA FRACTURE	SPIRAL FRACTURE RIGHT TIBIA	V59P6 (b) (6)
TIC	TICS NOS	V59P13 (b) (6)
TINEA CRURIS	TINEA CRURIS	V59P17 (b) (6)
TINEA INFECTION	RINGWORM	V59P6 (b) (6)
TINEA PEDIS	ATHLETE'S FOOT	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
TINEA VERSICOLOUR	PITYRIASIS VERSICOLOR	V59P11: (b) (6)
	TINEA VERSICOLOR	V59P13:
TINNITUS	TINNITUS	V59P17 (b) (6) V59P17 (b) (6)
TONSILLAR DISORDER	TONSIL PAIN	V59P18 (b) (6)
TONSILLAR HYPERTROPHY	TONSIL HYPERTROPHY	V59P13: (b) (6)
	TONSILLAR HYPERTROPHY	V59P18:
TONSILLITIS	TONSILLITIS	V59P11: (b) (6) V59P11: (b) (6) V59P11 (b) (6) V59P11: V59P11: V59P11 V59P11: V59P11: V59P11 V59P11: V59P11: V59P11: V59P11: V59P13: V59P17: (b) (6) V59P17: V59P17: (b) (6) V59P18: (b) (6) V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18: V59P18:
	TONSILLOPHARYNGITIS	V59P18: V59P18 (b) (6) V59P6 (b) (6)
TOOTH ABSCESS	ABSCESSED TOOTH	V59P13: (b) (6)
	DENTAL ABSCESS	V59P11: V59P13: (b) (6)
	TOOTH ABSCESS	V59P13: V59P17: (b) (6) V59P17 (b) (6)
TOOTH EXTRACTION	BACK TOOTH EXTRACTION	V59P18: (b) (6)
	CHEEK TOOTH EXTRACTION	V59P18:
	EXODONTIA (REMOVE OF A TOOTH FROM ITS SOCKET IN THE BONE)	V59P18:
	PROPHYLACTIC EXTRACTION OF MOLAR	V59P18 (b) (6)

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Note: Mappings done using MedDRA Version 10. Thesaurus.

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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TOOTH EXTRACTION	TEETH EXTRACTION	V59P13 (b) (6)
TOOTH INFECTION	DENTAL INFECTION	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6)
	INFECTED TOOTH	V59P13:
	MOLAR INFECTION	V59P17:
	TOOTH INFECTION	V59P18:
TOOTHACHE	ODONTALGIA	V59P11: (b) (6) V59P11 (b) (6)
	PAIN TOOTH	V59P11:
	TEETH PAIN	V59P13: V59P18: (b) (6) V59P18 (b) (6)
		V59P18: V59P18:
	TOOTH ACHE	V59P11: V59P11: (b) (6) V59P18 (b) (6)
		V59P18:
	TOOTH PAIN	V59P13: V59P13: (b) (6) V59P17 (b) (6)
		V59P17: V59P17:
	TOOTHACHE	V59P13: V59P13: V59P13 (b) (6)
		V59P13:
	TOOTHACHE (R) SIDE	V59P13:
	WISDOM TOOTH PAIN	V59P17:
TORTICOLLIS	TORTICOLLIS	V59P17: (b) (6) V59P18 (b) (6)
	WRYNECK	V59P11:
TRANSAMINASES INCREASED	TRANSAMINITIS	V59P13 (b) (6)
TRAUMATIC BRAIN INJURY	SEVERE CLOSED HEAD INJURY	V59P13 (b) (6)
TRAUMATIC TORTICOLLIS	TRAUMATIC TORTICOLLIS	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
TREMOR	BILATERAL HAND TREMORS	V59P6: (b) (6)
	LEGS TREMORS	V59P17: (b) (6)
	TREMORS	V59P13:
TRICHIASIS	TRICHIASIS	V59P13 (b) (6)
TUBERCULOSIS SKIN TEST POSITIVE	POSITIVE TUBERCULIN SKIN TEST	V59P13 (b) (6)
TYPE 2 DIABETES MELLITUS	DIABETES MELLITUS TYPE II UNCOMPLICATED	V59P13 (b) (6)
ULCERATIVE KERATITIS	CORNEAL ULCER	V59P13 (b) (6)
UMBILICAL HERNIA REPAIR	UMBILICAL HERNIORRHAPHY	V59P17 (b) (6)
UPPER LIMB FRACTURE	FRACTURE LEFT ARM	V59P13: (b) (6)
	LEFT ARM FRACTURE	V59P17: V59P6 (b) (6)
	OPEN ELBOW FRACTURE	V59P17:
UPPER RESPIRATORY TRACT INFECTION	SORE THROAT URI	V59P6: (b) (6)
	UPPER RESPIRATORY INFECTION	V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P17: V59P17: V59P17: V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6 (b) (6) V59P6: (b) (6) V59P6: V59P6 V59P6: V59P6: V59P6 V59P6:
	UPPER RESPIRATORY TRACT INFECTION	V59P17: (b) (6) V59P17: (b) (6) V59P17: (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers		
UPPER RESPIRATORY TRACT INFECTION	UPPER RESPIRATORY TRACT INFECTION	V59P17: (b) (6)	V59P18: (b) (6)	V59P18: (b) (6)
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P18:	V59P18:
		V59P18:	V59P6: (b) (6)	
	URI	V59P6: (b) (6)		
URINARY TRACT INFECTION	URINARY INFECTION	V59P17: (b) (6)	V59P17: (b) (6)	
	URINARY TRACT INFECTION	V59P13:	V59P13:	V59P13: (b) (6)
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P13:
		V59P13:	V59P13:	V59P17:
		V59P17:	V59P17:	V59P17:
		V59P17:	V59P17:	V59P18:
		V59P18:		
	UTI	V59P13:		
URTICARIA	ALLERGIC REACTION-HIVES (NOT AT INJECTION SITE)	V59P13: (b) (6)		
	HIVES	V59P13:	V59P13 (b) (6)	
	HIVES ON FACE	V59P6: (b) (6)		
	LEFT ARM HIVES	V59P13: (b) (6)		
	RASH/URTICARIA	V59P18:		
	URTICARIA	V59P11:	V59P11: (b) (6)	V59P11 (b) (6)
		V59P17:	V59P18: (b) (6)	
	URTICARIAL RASH	V59P17:		

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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URTICARIA	WELTS	V59P6 (b) (6)
UTERINE LEIOMYOMA	UTERINE MYOMATOSIS	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P17:
VACCINATION COMPLICATION	POSSIBLE VACCINE REACTION	V59P13 (b) (6)
VAGINAL DISCHARGE	VAGINAL DISCHARGE	V59P17: (b) (6) V59P17 (b) (6) V59P17 (b) (6) V59P17:
VAGINAL HAEMORRHAGE	VAGINAL BLEEDING	V59P13 (b) (6)
VAGINAL INFECTION	VAGINAL INFECTION	V59P13 (b) (6) V59P13 (b) (6) V59P17 (b) (6)
VAGINITIS BACTERIAL	BACTERIAL VAGINOSIS VAGINAL BACTERIAL INFECTION	V59P17: (b) (6) V59P13:
VARICELLA	CHICKENPOX	V59P11: (b) (6) V59P13: (b) (6) V59P17 (b) (6) V59P17: V59P18: (b) (6)
	VARICELLA	V59P11: V59P11: (b) (6)
VERTIGO	VERTIGO	V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P17: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P6: (b) (6)
VESSEL PUNCTURE SITE HAEMATOMA	BRUISE BLOOD DRAW SITE	V59P13 (b) (6)
VIRAEMIA	VIREMIA	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
VIRAL INFECTION	SYSTEMIC VIRAL ILLNESS	V59P13: (b) (6)
	VIRAL ILLNESS	V59P11: (b) (6) V59P11: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P13: (b) (6) V59P6: (b) (6)
	VIRAL INFECTION	V59P17: (b) (6) V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P17: V59P17: V59P17: V59P17: V59P17:
	VIRAL SYNDROME	V59P13:
	VIROSIS	V59P18:
VIRAL PHARYNGITIS	RHINOPHARYNGITIS (VIRAL)	V59P17: (b) (6)
	VIRAL PHARYNGITIS	V59P13: (b) (6) V59P13: (b) (6) V59P17 (b) (6) V59P17: V59P6: (b) (6)
	VIRAL RHINOPHARYNGITIS	V59P17:
VIRAL RASH	VIRAL EXANTHEM	V59P13 (b) (6)
VIRAL UPPER RESPIRATORY TRACT INFECTION	PROBABLE VIRAL UPPER RESPIRATORY INFECTION	V59P6 (b) (6)
VISION BLURRED	BLURRED VISION	V59P6 (b) (6)
VITELLO-INTESTINAL DUCT REMNANT	MECKEL'S DIVERTICULUM	V59P13 (b) (6)
VITILIGO	VITILIGO	V59P11 (b) (6)
VOMITING	EMESIS	V59P11: (b) (6) V59P11: (b) (6) V59P17 (b) (6) V59P17: V59P6:
	NAUSEA AND VOMITING	V59P13:
	VOMIT	V59P11: V59P17: (b) (6) V59P17: (b) (6) V59P17: V59P18: (b) (6) V59P18: (b) (6) V59P18: V59P18: V59P18:

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Summary of Verbatim to Preferred Term Mapping for Treatment-emergent Adverse Events

MedDRA Preferred Term	Verbatim Term	Protocol Numbers
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VOMITING	VOMITING	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P11: V59P13: V59P13: (b) (6) V59P13: (b) (6) V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P13: V59P17: V59P17: V59P18: V59P18: V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6) V59P6: (b) (6)
	VOMITUS	V59P11: (b) (6) V59P11: (b) (6) V59P11: (b) (6) V59P11: V59P17: V59P17: (b) (6)
VULVOVAGINAL BURNING SENSATION	BURN SENSATION IN VAGINA	V59P17 (b) (6)
VULVOVAGINAL MYCOTIC INFECTION	VAGINAL YEAST INFECTION	V59P13: (b) (6)
	VAGINOMYCOSIS	V59P17:
VULVOVAGINITIS TRICHOMONAL	VAGINAL INFECTION (TRICHOMONAS)	V59P17: (b) (6)
	VAGINAL TRICHOMONAS INFECTION	V59P17:
WEIGHT DECREASED	WEIGHT LOSS	V59P13 (b) (6)
WEIGHT INCREASED	ABNORMAL WEIGHT GAIN	V59P13: (b) (6)
	INCREASED WEIGHT	V59P13:
WHEEZING	WHEEZE	V59P13 (b) (6)
WHIPLASH INJURY	WHIPLASH	V59P13 (b) (6)

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MedDRA Preferred Term	Verbatim Term	Protocol Numbers
WISDOM TEETH REMOVAL	IMPACTED WISDOM TEETH EXTRACTION	V59P13: (b) (6)
	WISDOM TEETH PULLED	V59P13:
	WISDOM TEETH REMOVAL	V59P13: V59P13 (b) (6)
WOUND	HAND WOUND	V59P17: (b) (6)
	PUNCTURE WOUND	V59P13:
	PUNCTURE WOUND LEFT FOOT	V59P13:
	PUNCTURE WOUND-LEFT FOOT	V59P13:
	SECOND RIGHT FINGER WOUND	V59P17:
WOUND INFECTION	WOUND IN FACE INFECTED	V59P17: (b) (6)
	WOUND INFECTION	V59P6: (b) (6)
WRIST FRACTURE	BROKEN LEFT WRIST	V59P6: (b) (6)
	BROKEN WRIST	V59P13: (b) (6)
	FRACTURE LEFT WRIST	V59P6: (b) (6)
	FRACTURE WRIST	V59P13: (b) (6)
	FRACTURED LEFT WRIST	V59P13:
	LEFT WRIST FRACTURE	V59P11: V59P13 (b) (6)
	RIGHT WRIST FRACTURE	V59P11:

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Table 94. MenACWY SAEs Reported Through 15 FEB 2008 Outside of the Proposed Indication

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (µg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
V59P1	------	None	-------	-------	-------
V59P2	(b) (6)	Gastroenteritis	11 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Prolonged seizure	28 days	MenACWY (2.5-2.5-2.5-2.5 Ad+)	None
V59P3	(b) (6)	Lacunar tonsillitis	17 days	MenACWY (10-10-10-10 Ad+)	None
V59P4	(b) (6)	Pneumonia	55 days	MenACWY (5-5-5-5 Ad+)	None
		Reactive airway disease, worsening	52 days	MenACWY (5-5-5-5 Ad+)	None
	(b) (6)	Asthma attack	282 days	MenACWY (5-5-5-5 Ad+)	None
	(b) (6)	Peanut allergy	301 days	MenACWY (10-10-10-10 Ad-)	None
	(b) (6)	Gastroenteritis	74 days	MenACWY (10-10-10-10 Ad-)	None
		Dehydration	75 days	MenACWY (10-10-10-10 Ad-)	None
	(b) (6)	Acute gastroenteritis	464 days	MenACWY (5-5-5-5 Ad-)	None
	(b) (6)	Gastroenteritis	47 days	MenACWY (10-10-10-10 Ad-)	None
		Dehydration	48 days	MenACWY (10-10-10-10 Ad-)	None
	(b) (6)	Type I diabetes	50 days	MenACWY (10-10-10-10 Ad-)	None
		Esophageal stricture	89 days	MenACWY (10-10-10-10 Ad-)	None
		Esophageal perforation	124 days	MenACWY (10-10-10-10 Ad-)	None
		Esophageal stricture	93 days	MenACWY (10-10-10-10 Ad-)	None
		Esophageal stricture	109 days	MenACWY (10-10-10-10 Ad-)	None
	(b) (6)	Asthma	40 days	MenACWY (5-5-5-5 Ad-)	None
		Pneumonia	40 days	MenACWY (5-5-5-5 Ad-)	None
V59P5[a]	(b) (6)	Crush Injury, status post amputation right little toe	186 days	Menjugate® (10 Ad+)+ MenACWY(10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	34 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Hirschsprung's Disease	23 days	MenACWY (10-5-5-5 Ad+)	None
		Gastroenteritis on background of Hirschsprung's Disease	55 days	MenACWY (10-5-5-5 Ad+)	None
		Gastroenteritis on background of Hirschsprung's Disease	113 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Urinary retention	153 days	MenACWY (10-5-5-5 Ad+)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Release of tendons on right hand, correction of trigger finger	36 days	Menjugate® (10 Ad+)+ MenACWY(10-5-5-5 Ad+)	None
	(b) (6)	Viral illness	16 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Viral infection	150 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Skin tag on lumbar region, removal-elective hospitalization following surgery	91 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Gastroesophageal reflux	19 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Afebrile seizures	54 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Croup	163 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Hypospadias	35 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Idiopathic thrombocytopenic purpura	7 days	MenACWY (10-5-5-5 Ad+)	Possibly related
	(b) (6)	Petechial rash	28 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Viral infection	32 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Accidental injury, fractured right femur	139 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Plagiocephaly	258 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Viral rash	104 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	50 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	28 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Viral gastroenteritis	133 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Febrile convulsion	165 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Chest infection	372 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	1 days	MenACWY (10-5-5-5 Ad+)	None
		Viral induced wheeze	80 days	MenACWY (10-5-5-5 Ad+)	None
		Probable viral illness	182 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Febrile convulsion	24 days	MenACWY 10-5-5-5 (Ad+)	None
	(b) (6)	Allergic reaction to food	39 days	MenACWY 10-5-5-5 (Ad+)	None
	(b) (6)	Viral infection	189 days	MenACWY 10-5-5-5 (Ad+)	None
	(b) (6)	Benign superficial cyst	219 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Supraventricular Tachycardia (SVT) secondary to inability to tolerate usual prophylaxis due to gastroenteritis	36 days	MenACWY (10-5-5-5 Ad+)	None
		Supraventricular Tachycardia (SVT)	5 hrs 50 min	MenACWY (10-5-5-5 Ad+)	Possibly related
	(b) (6)	Gastroenteritis	141 days	MenACWY (10-5-5-5 Ad+)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Pneumonia	1 day	MenACWY (10-5-5-5 Ad+)	None
		Pneumonia	82 days	MenACWY (10-5-5-5 Ad+)	None
		Chest infection	411 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Infected congenital pulmonary cyst	110 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Viral illness	63 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	22 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Pneumonia	167 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Inguinal hernia	8 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	18 days	MenACWY (10-5-5-5 Ad+)	None
		Viral respiratory infection	About 4 weeks	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Infected chickenpox	163 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	2 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	First degree burns	61 days	MenACWY (10-5-5-5 Ad-)	None
		Upper respiratory tract infection	65 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Developmental delay	10 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Head injury	276 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Influenza	63 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis secondary to RSV	217 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	50 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Suspicion of septic arthritis left hip	188 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Possible developmental delay	3 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Viral gastroenteritis	53 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Erythema multiforme	119 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Febrile seizure	205 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
	(b) (6)	Vomiting - unknown cause	202 days	MenACWY (10-5-5-5 Ad+)+ Menomune (50-50-50-50)	None
	(b) (6)	Viral illness	150 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Bronchiolitis	39 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Second degree burn to right hand	190 days	MenACWY (10-5-5-5 Ad+)+ Menomune (50-50-50-50)	None
	(b) (6)	Fractured right femur	378 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Asthma	89 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	30 days	MenACWY (10-5-5-5 Ad-)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Bronchiolitis	3 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Asthma	393 days	MenACWY (10-5-5-5 Ad-)+ Menomune (50-50-50-50)	None
	(b) (6)	Croup	155 days	MenACWY (10-5-5-5 Ad-)+Menomune (50-50-50-50)	None
		Croup	269 days	MenACWY (10-5-5-5 Ad-)+Menomune (50-50-50-50)	None
	(b) (6)	GERD with secondary aspiration	177 days	MenACWY (10-5-5-5 Ad-)+Menomune (50-50-50-50)	None
	(b) (6)	Bilateral inguinal herniae repair (Hydrocele)	5 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Reactive airway disease	399 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
		Viral Infection	399 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
	(b) (6)	Salmonella infection	6 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Respiratory synctial virus infection	5 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
	(b) (6)	Respiratory synctial virus bronchiolitis	10 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Croup	363 days	MenACWY (10-5-5-5 Ad-)+Menomune (50-50-50-50)	None
	(b) (6)	Bilateral inguinal hernia repair	9 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
		Left hydrocele repair	9 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
		Circumcision	9 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
		Mild bronchiolitis	12 days	MenACWY (10-5-5-5 Ad+)+Menomune (50-50-50-50)	None
	(b) (6)	Reactive airway disease	318 days	MenACWY (10-5-5-5 Ad-)+Menomune (50-50-50-50)	None
V59P7	(b) (6)	Varicella	220 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Chickenpox	2 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	87 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	288 days	MenACWY (10-5-5-5 Ad-)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Varicella	10 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Varicella	249 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Otitis media	128 days	MenACWY (10-5-5-5 Ad+)	None
		Suspected pneumonia	128 days	MenACWY (10-5-5-5 Ad+)	None
		Acute gastroenteritis	129 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Febrile convulsion	18 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Inguinal hernia, right	About 8 weeks	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	140 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Kawasaki's disease	147 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Vulnus manus on right finger no. V	43 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	128 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	138 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	313 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	165 days	Mencevax (50-50-50-50)/ MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Fracture of left humerus	67 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	154 days	Mencevax (50-50-50-50)/ MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Chickenpox	120 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	About 5 months	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Infection of lower jaw region after mandibular biopsy	57 days	Mencevax (50-50-50-50)/ MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	48 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Concussion of the brain	80 days	Mencevax (50-50-50-50)/ MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	78 days	Mencevax (50-50-50-50)/ MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Cerebral tumor of the posterior cavity	36 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Acute gastroenterocolitis	17 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Acute enterocolitis	46 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Varicella	142 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Epiglottitis	221 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	148 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Varicella	12 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	312 days	MenACWY (10-5-5-5 Ad-)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Left nephrolithiasis	233 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute laryngitis	245 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute gastroenterocolitis	163 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Varicella	258 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Diabetes mellitus	89 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Varicella	310 days	MenACWY (10-5-5-5 Ad+)	
	(b) (6)	Acute Gastroenteritis	1 day	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Varicella	14 days	MenACWY (10-5-5-5 Ad+)	None
	(b) (6)	Laryngitis	30 days	MenACWY (10-5-5-5 Ad-)	None
V59P8	(b) (6)	Pneumonia	48 days	MenACWY (10-5-5-5 Ad-)	None
		Hypoxia	48 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Reactive airway disease	110 days	MenACWY (10-5-5-5 Ad-)	None
		Pneumonia	112 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Dehydration secondary to diarrhea	31 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Obstructive sleep apnea	261 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Possible febrile seizure	34 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Gastroenteritis	233 days	MenACWY (10-5-5-5 Ad-)	None
		Dehydration	233 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Asthma	237 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Febrile seizure	39 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Herpes simplex gingivostomatitis	67 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Cellulitis, left lower leg	152 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute appendicitis	336 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pneumonia, left lower lobe	253 days	MenACWY (10-5-5-5 Ad-)	None
		Left sided pleural effusion	256 days	MenACWY (10-5-5-5 Ad-)	None
		Left sided empyema	249 days	MenACWY (10-5-5-5 Ad-)	None
		Left Hydropneumothorax	271 days	MenACWY (10-5-5-5 Ad-)	None
V59P9	(b) (6)	Asthma	115 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	170 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Lethargy	121 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Respiratory syncytial virus infection	125 days	MenACWY (10-5-5-5 Ad-)	None
V59P10[b]	(b) (6)	Pneumonia	47 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Appendicitis	6 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Skull traumatism	122 days	MenACWY (10-5-5-5 Ad-)/Menomune	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Febrile seizure	18 hrs 50 min	MenACWY (10-5-5-5 Ad-)/Menomune	Possibly related
	(b) (6)	Pneumonia	30 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Pneumonia	12 hrs 43 min	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Asthma crisis	96 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Post vaccinal tonic convulsion	15 min	MenACWY (10-5-5-5 Ad-)/Menomune	Study Conduct Related
	(b) (6)	Lobar pneumoniae	2 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
	(b) (6)	Acute appendicitis	139 days	MenACWY (10-5-5-5 Ad-)/Menomune	None
V59P14[c]	(b) (6)	Bronchiolitis	25 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Fracture left elbow (closed)	25 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bloody stool (one-time)	8 hrs 20 min	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pyloric stenosis	15 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Choking spell secondary to GERD	10 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pertussis	5 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Respiratory syncytial virus bronchiolitis	84 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	76 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	52 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	RSV bronchiolitis	59 days	MenACWY (10-5-5-5 Ad-)	None
		Hypoxia	59 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	RSV positive, bronchiolitis	21 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Respiratory syncytial virus	4 days 10 hrs	MenACWY (10-5-5-5 Ad-)	None
		Pneumonia	4 days 10 hrs	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Viral illness	62 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	48 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Second degree scald burn to left leg	42 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Subarachnoid hemorrhage	38 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Worsening of scabies	6 hrs 45 min	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Gastroenteritis	49 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Respiratory infection	30 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Exanthema subitum	51 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Fever	24 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Mononucleosis	24 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Botulism	1 day	MenACWY (10-5-5-5 Ad-)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (μg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Atypical pneumonia	27 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	40 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute bronchitis	33 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pneumonia	37 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bacterial pneumonia	7 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pneumonia	7 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Head trauma	42 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Urinary tract infection	40 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Urinary tract infection	23 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bacterial pneumonia	45 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pneumonia	48 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute diarrhea	18 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	24 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Skin abscess	7 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	52 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	35 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute bronchiolitis	58 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Viral gastroenteritis	65 days	MenACWY (10-5-5-5 Ad-)	None
		Acute bronchiolitis	98 days	MenACWY (10-5-5-5 Ad-)	None
		Acute media otitis	98 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	33 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Febrile syndrome	46 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bacterial diarrhoea with dehydration	46 days	MenACWY (10-5-5-5 Ad-)	None
		Pneumonia	46 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Left cellulitis preseptal	30 days	MenACWY (10-5-5-5 Ad-)	None
		Blepharitis	30 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pertussis like syndrome	29 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchopneumonia	29 days	MenACWY (10-5-5-5 Ad-)	None
		Bacterial diarrhoea	29 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Pneumonia	47 days	MenACWY (10-5-5-5 Ad-)	None
V59P16[c]	(b) (6)	Gastroenteritis	20 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	12 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Viral illness	33 days	MenACWY (10-5-5-5 Ad-)	None

Protocol	Subject ID	Condition Verbatim	Onset from last vaccination*	Vaccine Group (µg Ag Content) (Adjuvant+/-)	Relationship to Study Vaccine
	(b) (6)	Viral illness	27 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Bronchiolitis	22 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Haematemesis	22 days	MenACWY (10-5-5-5 Ad-)	None
V59P18[c]	(b) (6)	Traffic accident	67 days	MenACWY (10-5-5-5 Ad-)	None
	(b) (6)	Acute appendicitis	131 days	MenACWY (10-5-5-5 Ad-)	None

Ad+ = with adjuvant, Ad- = without adjuvant
* The onset from last vaccination refers to the time or the number of days between the reported onset of the SAE and the last MenACWY vaccination given to the subject.
a For subjects who also received Menomune, one reduced dose (one-fifth of the full dose content) was given.
b Group unblinded only
c Study ongoing; for V59P18, only events reported after interim CSR visit 3

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THIS REPORT MAY CONTAIN CONFIDENTIAL INFORMATION

STN: L 125300/0

Applicant: GlaxoSmithKline Biologicals #1617

Product: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine

Short Summary: active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135 when administered to individuals 11 through 55 years of age

Date	Elec	Post	Description	FDA Recd Date	Login ID
05-SEP-2008	Y		Letter. Acknowledgement Letter (DICKERSON, DAVID)		
05-SEP-2008	Y		Memo. Review Committee Assigned Memorandum (VANN, WILLIE)		
17-SEP-2008	Y	Y	Meeting Summary. First Committee Meeting - First Meeting Summary/ Committee Meeting Minutes (FIORE, CARA)		
13-OCT-2008	Y	Y	Meeting Summary. Filing Meeting Summary - Held Via Email. (VANN, WILLIE)		
21-OCT-2008	Y	Y	Letter. Filing Notification Letter (DICKERSON, DAVID)		
22-OCT-2008	Y	Y	Meeting Summary. Committee Meeting Summary - See EDR for October meeting summary. (FIORE, CARA)		
23-OCT-2008	Y		Memo. Change In Review Committee Assignment - Addition of: Milan Blake, Nicolette deVore, David Menschik, Tina Roecklein, Elizabeth Valenti Removal of: Jane Woo, Chris Lynch (VANN, WILLIE)		
07-NOV-2008	Y	Y	Letter. Deficiencies Identified (FIORE, CARA)		
18-NOV-2008	Y	Y	Meeting Summary. Committee Meeting Summary - Summary of November Monthly Meeting (FIORE, CARA)		
26-NOV-2008	Y		Telecon. Information Request - Clarification of production schedule during upcoming inspection (TRUDEL, NICOLE)		
17-DEC-2008	Y	Y	Meeting Summary. Committee Meeting Summary - December Monthly Meeting Summary (FIORE, CARA)		
07-JAN-2009	Y	Y	Telecon. Information Request - EMAIL Linearity and Final Container Questions (FIORE, CARA)		
12-JAN-2009	Y	Y	Memo. Committee Memo/Review - Mid-cycle review DT assay validation (MEYSICK, KAREN)		
16-JAN-2009	Y	Y	Telecon. Information Request - FAX: Comments on the assay validation of Diptheria and Tetanus concomitant vaccines (FIORE, CARA)		
27-JAN-2009	Y	Y	Telecon. Information Request - EMAIL CBER concurs to rerun statistical analysis for PRN in V59P18 using LLQ and request for data from the proposed re-analysis of the PRN ELISA (VALENTI, ELIZABETH)		
29-JAN-2009	Y	Y	Telecon. Information Request - PVP Comments (VALENTI, ELIZABETH)		
04-FEB-2009	Y		Telecon. Advice - EMAIL No Nato # on PI (VALENTI, ELIZABETH)		
05-FEB-2009	Y	Y	Memo. Committee Memo/Pharm-tox Review - Based on nonclinical toxicity assessments of this study, there are no significant safety issues to preclude the BLA from going into effect. (AL-HUMADI, NABIL)		
06-FEB-2009	Y		Memo. Committee Memo/Review - APLB review of PI. (MILLER, CATHERINE)		
06-FEB-2009	Y		Telecon. Advice - EMAIL: Info re product release samples and USDA Import Form (VALENTI, ELIZABETH)		
06-FEB-2009	Y		Telecon. Advice - EMAIL: Info re sample submission and USDA Import Form. Novartis submitting lot release protocol today. (VALENTI, ELIZABETH)		
11-FEB-2009	Y	Y	Meeting Summary. Committee Meeting Summary - February Monthly Team Meeting (VALENTI, ELIZABETH)		
17-FEB-2009	Y		Telecon. Advice - Correction from previous email are the words "two...each" to "Yes, monovalent conjugates for each of 4 types, two containers of 25 ml each (rather than 10 - 20 ml) from each of 3 lots used in the manufacture of DP samples" (FIORE, CARA)		
27-FEB-2009	Y		Memo. Committee Memo/Review - APLB review of carton & container labels. (MILLER, CATHERINE)		
06-MAR-2009	Y	Y	Memo. Review - Pertussis assay validation review (BURNS, DRUSILLA)		
11-MAR-2009	Y	Y	Meeting Summary. Committee Meeting Summary - March Monthly Team Meeting (VALENTI, ELIZABETH)		

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STN: L 125300/0

Applicant: GlaxoSmithKline Biologicals #1617

Product: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine

Short Summary: active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135 when administered to individuals 11 through 55 years of age

Date	Elec	Post	Description	FDA Recd Date	Login ID
23-MAR-2009	Y	Y	Telecon. Advice - Advised Novartis that process validation must be in place for all 4 strains prior to approval. (VALENTI, ELIZABETH)		
25-MAR-2009	Y	Y	Memo. Review - DT ELISA Assay Validation (MEYSICK, KAREN)		
03-APR-2009	Y		Telecon. Advice - EMAIL: Submit Batch Protocol and Data with samples and to BLA. (VALENTI, ELIZABETH)		
04-APR-2009	Y	Y	Memo. Committee Memo/Review (LEE, ROBERT)		
06-APR-2009	Y	Y	Telecon. Information Request - PREA Info (VALENTI, ELIZABETH)		
08-APR-2009	Y	Y	Meeting Summary. Committee Meeting Summary - April monthly internal meeting summary (FIORE, CARA)		
27-APR-2009	Y		Telecon. Information Request - Email: List of Reagents and documents needed for in-support testing. (VALENTI, ELIZABETH)		
01-MAY-2009	Y	Y	Memo. Review / Committee Memo/Pharm-tox Review - See EDR for review memo. (GRUBER, MARION)		
01-MAY-2009	Y		Telecon. Advice - packaging and carton advice (FIORE, CARA)		
01-MAY-2009	Y	Y	Telecon. Information Request - requested 24 month stability data for final product (FIORE, CARA)		
04-MAY-2009	Y	Y	Telecon. Information Request - requested again 24 month stability data (both requested via email) (FIORE, CARA)		
07-MAY-2009	Y		Telecon. Advice - Informed Novartis that additional information is needed to complete review CP for (b) (4) fill line. Additionally, informed firm that CBE-30 reporting category is acceptable. (GEORGE, JOSEPH)		
13-MAY-2009	Y		Telecon. Advice - 1) They will be submitted new stability data and the revised packaging/carton mock up by the end of next week. 2) Labeling - they are planning an add campaign and want to know when to expect our labeling comments. 3) They stated that we had said we woul (FIORE, CARA)		
13-MAY-2009	Y	Y	Telecon. Advice - Pharmacovigilance comments on their response to our comments send via email. (FIORE, CARA)		
22-MAY-2009	Y	Y	Telecon. Information Request - Email: Manufacturing and product IRs (FIORE, CARA)		
04-JUN-2009	Y		Memo. Test Results - Moisture test results - Men A drug product (DEL GROSSO, ALFRED)		
12-JUN-2009	Y	Y	Memo. Committee Memo - Bioresearch Monitoring Inspection Results (WHITE, JANET)		
12-JUN-2009	Y	Y	Telecon. Advice - Submission of CR response & CSR for V59P13E1 (FIORE, CARA)		
16-JUN-2009	Y		Memo. Review - container & carton labels. (STEWART, DAPHNE)		
22-JUN-2009	Y		Memo. Committee Memo - Categorical exclusion from Environmental Assessment is justified. (GEORGE, JOSEPH)		
22-JUN-2009	Y		Memo. Committee Memo/Testing Summary - Sterility and Endotoxin Test Results (KENNEY, JAMES)		
24-JUN-2009	Y	Y	Memo. Committee Memo/Review - Facilities/CMC review (GEORGE, JOSEPH)		
24-JUN-2009	Y		Memo. Review - container & carton labels. (STEWART, DAPHNE)		
24-JUN-2009	Y	Y	Memo. Review - Facility/Equipment CMC first0cycle review memo (TRUDEL, NICOLE)		
24-JUN-2009	Y	Y	Telecon. Information Request - Email: Equipment cleaning validation (FIORE, CARA)		
25-JUN-2009	Y	Y	Letter. Complete Response (FIORE, CARA)		
29-JUN-2009	Y		Telecon. Advice - C. Fiore answered some sponsor questions regarding CR responses (FIORE, CARA)		
09-JUL-2009	Y		Telecon. Advice - CP for Filling Line (FIORE, CARA)		
17-JUL-2009	Y		Telecon. Information Request - Test Lots Information Request (FIORE, CARA)		

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Date	Elec	Post	Description	FDA Recd Date	Login ID
24-JUL-2009	Y		Telecon. Advice - Submission of launch lots for testing; See EDR for details (FIORE, CARA)		
10-AUG-2009	Y	Y	Telecon. Advice / Information Request - PVP for Menveo; See EDR for details (FIORE, CARA)		
09-SEP-2009	Y		Telecon. Information Request - Request for Men A Standard (FIORE, CARA)		
09-OCT-2009	Y	Y	Letter. Resubmission Acknowledgement Letter (DICKERSON, DAVID)		
14-OCT-2009	Y	Y	Meeting Summary. Committee Meeting Summary - October 2009 Monthly Internal Meeting Summary (FIORE, CARA)		
14-OCT-2009	Y		Telecon. Advice - A016 Proposal for Testing (FIORE, CARA)		
14-OCT-2009	Y		Telecon. Advice - advice regarding launch lots and pre-licensure testing (FIORE, CARA)		
15-OCT-2009	Y	Y	Telecon. Other - Leachable in stopper (AL-HUMADI, NABIL)		
03-NOV-2009	Y	Y	Telecon. Advice - 36 month dating and PVP plan (FIORE, CARA)		
12-NOV-2009	Y		Memo. Change In Review Committee Assignment - remove M. Lee and D. Menschik. add D. Martin. (VANN, WILLIE)		
12-NOV-2009	Y	Y	Meeting Summary. Committee Meeting Summary - November team meeting summary (VALENTI, ELIZABETH)		
17-NOV-2009	Y		Telecon. Labeling via FAX/e-mail - Marked up carton & container labels faxed to the sponsor. (FIORE, CARA)		
20-NOV-2009	Y		Telecon. Labeling via FAX/e-mail / Advice - Carton & container discussion (VALENTI, ELIZABETH)		
20-NOV-2009	Y		Telecon. Labeling via FAX/e-mail - Use of MENVEO (r) (VALENTI, ELIZABETH)		
01-DEC-2009	Y		Telecon. Labeling via FAX/e-mail - Use of hyphen between W and 135 (FIORE, CARA)		
14-DEC-2009	Y	Y	Telecon. Information Request - Drug substance testing (FIORE, CARA)		
16-DEC-2009	Y	Y	Meeting Summary. Committee Meeting Summary - Committee Meeting Summary (FIORE, CARA)		
17-DEC-2009	Y	Y	Memo. Review - Comments on Draft Clinical Study Protocol V59_34: ¿A Phase IV study to assess the safety of MenACWY vaccine being used by HMO subjects aged 11-19 years of age¿ (MARTIN, DAVID)		
18-DEC-2009	Y	Y	Telecon. Advice - Lot Release protocol, lot release template, sialic acid and formaldehyde testing discussed. (FIORE, CARA)		
23-DEC-2009	Y	Y	Telecon. Information Request / Advice - CBER Comments on PVP (V59P34) (FIORE, CARA)		
23-DEC-2009	Y		Telecon. Advice - Package insert labeling comments conveyed by email to sponsor (FIORE, CARA)		
24-DEC-2009	Y		Memo. Review - Labeling (STEWART, DAPHNE)		
29-DEC-2009	Y		Memo. PNR 90 Day Evaluation - Re-evaluation of proposed proprietary name within 90 days of application's action due date. (MILLER, CATHERINE)		
07-JAN-2010	Y	Y	Telecon. Advice - Pharmacoviglance plan comments conveyed over a telecon to sponsor (FIORE, CARA)		
08-JAN-2010	Y		Telecon. Advice - Carton container comments conveyed by telecon (FIORE, CARA)		
12-JAN-2010	Y		Memo. Committee Memo/Testing Summary - Sterility and Endotoxin Test Results (KENNEY, JAMES)		
13-JAN-2010	Y	Y	Memo. Committee Memo/Statistical Review - Statistical Review Memo (KRASNICKA, BARBARA)		
20-JAN-2010	Y	Y	Meeting Summary. Committee Meeting Summary - January Review Committee Meeting Summary (FIORE, CARA)		

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Date	Elec	Post	Description	FDA Recd Date	Login ID
20-JAN-2010	Y		Telecon. Labeling via FAX/e-mail - Combined comments for MENVEO USPI (BASH, MARGARET)		
21-JAN-2010	Y		Memo. Test Results - Identity Test Results (JOSHI, MANJU)		
22-JAN-2010	Y		Memo. Request For Compliance Check (GEORGE, JOSEPH)		
22-JAN-2010	Y		Memo. Test Results - Chemistry Test Results (DEL GROSSO, ALFRED)		
25-JAN-2010	Y	Y	Memo. Review - Pharmacovigilance plan review. (MARTIN, DAVID)		
25-JAN-2010	Y	Y	Telecon. Advice - PVP Date (VALENTI, ELIZABETH)		
25-JAN-2010	Y	Y	Telecon. Advice / Labeling via FAX/e-mail / Other - Acceptance of Safety PMC completion date. Proposed PMC for concom immune interference No further comments on carton & container (VALENTI, ELIZABETH)		
26-JAN-2010	Y	Y	Memo. Committee Memo/Review - Review of IR responses to filling Line (b) (4) (b) (4) CP. (GEORGE, JOSEPH)		
27-JAN-2010	Y	Y	Memo. Committee Memo/Review - DPQ Review Memo/Recommend approval (GUPTA, RAJESH)		
27-JAN-2010	Y		Memo. Committee Memo/Statistical Review - Statistical Review-Label (KRASNICKA, BARBARA)		
27-JAN-2010	Y		Memo. Compliance Check Completed - DCM does not object to approval. (ALSTON, MARC)		
27-JAN-2010	Y	Y	Telecon. Information Request - Define date of manufacture, launch lot # and updated specifications to be sent to BLA (FIORE, CARA)		
29-JAN-2010	Y		Telecon. Labeling via FAX/e-mail - Labeling comments. (FIORE, CARA)		
29-JAN-2010	Y		Telecon. Advice - UNII Code (VALENTI, ELIZABETH)		
02-FEB-2010	Y	Y	Memo. Committee Memo/Review - Clinical Review Memo (BASH, MARGARET)		
02-FEB-2010	Y	Y	Memo. Committee Memo/Review - CMC Review (LEE, ROBERT)		
03-FEB-2010	Y		Memo. Test Results - CBER Test Results for total saccharide and hydrodynamic size (DEL GROSSO, ALFRED)		
04-FEB-2010	Y		Telecon. Advice - Discussion of the package insert revisions, except section 14 (clinical studies). Novartis has embedded comments in this version. (FIORE, CARA)		
05-FEB-2010	Y		Telecon. Other - Routine stability testing. (VALENTI, ELIZABETH)		
12-FEB-2010	Y	Y	Memo. Committee Memo/Review - Analytical Test Method Validation Report (BLAKE, MILAN)		
12-FEB-2010	Y	Y	Telecon. Advice - future changes to stability protocol should be submitted as a PAS. (VALENTI, ELIZABETH)		
16-FEB-2010	Y		Telecon. Labeling via FAX/e-mail (MARSHALL, VALERIE)		
17-FEB-2010	Y	Y	Memo. Committee Memo/Review (FREEDBERG, DARON)		
17-FEB-2010	Y		Telecon. Other - Officer Employee List: original email and all responses (VALENTI, ELIZABETH)		
17-FEB-2010	Y		Telecon. Labeling via FAX/e-mail - USPI V7 Track Changes (FIORE, CARA)		
17-FEB-2010	Y		Telecon. Labeling via FAX/e-mail - USPI (FIORE, CARA)		
18-FEB-2010	Y	Y	Memo. Committee Memo/Statistical Review - Statistical Review Revision (HORNE, AMELIA DALE)		
18-FEB-2010	Y		Telecon. Labeling via FAX/e-mail - Menveo USPI V8 tracked changes 021810 (FIORE, CARA)		
19-FEB-2010	Y	Y	Memo. Committee Memo/Review - Addendum to the January 22, 2010 Pharmacovigilance Plan Review (NGUYEN, MICHAEL)		
19-FEB-2010	Y		Memo. Licensing Action Recommendation Memo (LARM) (DICKERSON, DAVID)		
19-FEB-2010	Y		Memo. Other - Lot Release Testing Plan (CAMPBELL, KAREN)		

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19-FEB-2010	Y	Y	Memo. Review - SBRA (VANN, WILLIE)		
19-FEB-2010	Y		Letter. Approval (FIORE, CARA)		
19-FEB-2010	Y		Telecon. Other - Telecon re: vial labels (VALENTI, ELIZABETH)		
11-MAR-2010	Y	Y	Memo. Other - List of consenting officers and employees. (VALENTI, ELIZABETH)		
28-AUG-2008	Y		Original Application. active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135 when administered to individuals 11 through 55 years of age	29-AUG-2008	448295
21-NOV-2008	Y		Amendment # 1. CMC: Extractables/Leachables	21-NOV-2008	453650
05-DEC-2008	Y		Amendment # 2. Update of SAEs in study V59P18 (interim report submitted in 125300/0.0)	05-DEC-2008	454409
19-DEC-2008	Y		Amendment # 3. First response to CBER's DI Letter	19-DEC-2008	455482
15-JAN-2009	Y		Amendment # 4. Second response to Deficiency Letter	15-JAN-2009	456886
06-FEB-2009	Y		Amendment # 5. Responses to CBER¿s Requests for Information; Final Container and Drug Substance Protocol; Revised Facility Floor Plan and Materials Flow; Revised Packaging Mock-Ups; Final Data from Study V59P13; and Final Data from Study V59P17	06-FEB-2009	458213
24-FEB-2009	Y		Amendment # 6. Report on Study V59P18	24-FEB-2009	459348
09-MAR-2009	Y		Amendment # 7. Responses to Pharmacovigilance Issues	09-MAR-2009	460258
30-MAR-2009	Y		Amendment # 8. Correction of Expressions of Action and Alert Limits and Updated List of Products Formulated and/or Filled in Building (b) (4) at the Rosia Site.	30-MAR-2009	461630
10-APR-2009	Y		Amendment # 9. Request for Deferral of Pediatric Studies	10-APR-2009	462523
17-APR-2009	Y		Amendment # 10. Response to Form FDA-483 Observations	17-APR-2009	462928
06-MAY-2009	Y		Amendment # 11. Batch Production Records and Documents Provided with Product Samples Submitted for Pre-Licensure Testing	06-MAY-2009	464183
15-MAY-2009	Y		Amendment # 12. updated stability data and revised packaging Mock-Ups	15-MAY-2009	464826
17-JUN-2009	Y		Amendment # 13. Revalidation of Polysaccharide (b) (4)	17-JUN-2009	466965
22-JUN-2009	Y		Amendment # 14. Responses to CBER¿s Information Request on New Filling Line (b) (4) and Product Details	22-JUN-2009	467234
21-AUG-2009	Y		Amendment # 15. Class 2 Resubmission to CBER's CR letter dated June 25, 2009	21-AUG-2009	471323
08-OCT-2009	Y		Amendment # 16. Information Amendment: Proposal on Submission of Pre-Licensure Samples for Testing	08-OCT-2009	474469
25-NOV-2009	Y		Amendment # 17. (b) (4) Drug Product Stability Data to 36 Months After Release; Batch Data for Samples Sent for Pre-Licensure Testing; Draft Protocol for Post-Licensure Pharmacovigilance Study	25-NOV-2009	477719
15-DEC-2009	Y		Amendment # 18.	15-DEC-2009	478986
15-JAN-2010	Y		Amendment # 19. revised labeling and postmarketing information	15-JAN-2010	480717
09-FEB-2010	Y		Amendment # 20. Revised USPI Versions 4, 5 and 6; Final MenACYW-135 Batch Release Protocol Template; Batch Analyses MenW-CRM batches (b) (4) and (b) (4)	09-FEB-2010	482093
19-FEB-2010	Y		Amendment # 22. revised PI	19-FEB-2010	482823

2.0 SYNOPSIS

Name of Sponsor/Company Chiron Vaccines	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine	**Volume:** **Page:**	
Name of Active Ingredient Men A-CRM_{197}conjugate, Men C-CRM_{197}conjugate, Men W_{135}-CRM_{197}conjugate, Men Y-CRM_{197}conjugate	**Study number: V59P1**	

Title of study: A Phase I, Open Label, Randomized, Single Center, Active Controlled Study to Evaluate Safety and Immunogenicity of One Dose of Either Chiron Meningococcal Conjugate ACWY Vaccine, or Separate but Concomitant Administration of the Lyophilized Meningococcal A Component Reconstituted with Aluminum Phosphate as Adjuvant and Meningococcal CWY Full Liquid Vaccine, or Polysaccharide Meningococcal ACWY Vaccine (GSK Mencevax®), in Healthy Adult Subjects

Investigator: Silvio Crestani, MD

Study center: Institute for Pharmacokinetic and Analytical Studies,Via Mastri 36, CH - 6853 Ligornetto, Switzerland

Publication (reference): None

Study period: 2002 (7 NOV – 11 DEC)	**Phase of development:** Phase I

Objectives:

Primary objective

The primary objective of the study was to evaluate the safety of a single dose of Chiron Men ACWY, Chiron Men A+CWY and GSK Mencevax® (control) vaccines.

Secondary objectives

In each vaccination group the evaluation of immunogenicity was performed by calculating for each serogroup:

- Serum Bactericidal Activity (SBA) GMT increases at 28-35 days after vaccination compared with baseline values (day 1).
- The percentage of subjects with SBA titer ≥ 1:4 before (day 1) and 28-35 days after vaccination.
- The ¯ercenta¯e of sub·ects with SBA titer ≥ 1:8 ┗efore ‘da¯· 1’ and 28-35 da¯s after

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vaccination.

- The percentage of subjects with a 4-fold increase of SBA titers 28-35 days after vaccination.
- ELISA (total IgG) GMTs before (day 1) and 28-35 days after vaccination.

Methodology:

A total of approximately 90 healthy adult subjects were to be enrolled and randomized in a 1:1:1 ratio to receive one dose of either Chiron Men ACWY or Chiron Men A+CWY or GSK Mencevax® (control) vaccine according the following scheme:

Group 1: 30 subjects to receive Chiron Men ACWY vaccine

Group 2: 30 subjects to receive Chiron Men A+CWY vaccine

Group 3: 30 subjects to receive GSK Mencevax® (control) vaccine

Subjects were screened to ensure they were in good health and met all inclusion criteria and no exclusion criteria. Medical history was obtained and a physical examination performed. Blood and urine samples were obtained for standard clinical laboratory tests prior to inclusion. At visit 1 a blood sample was taken before the vaccination. Chiron Men ACWY and Chiron Men A+CWY vaccines were administered intramuscularly (IM) in the deltoid region, GSK Mencevax® (control) vaccine was administered subcutaneously (SC) in the deltoid region.

Subjects remained in the clinic for 60 minutes after vaccination. After 60 minutes, subjects were evaluated for any immediate local and systemic reactions and other adverse events. The subjects were then instructed to complete diary cards to describe local reactions (i.e., ecchymosis, erythema, induration, swelling and pain), systemic reactions (i.e., malaise, chills, headache, nausea, myalgia and arthralgia) and other indicators of reactogenicity (i.e., axillary temperature measurements, taking of analgesics/antipyretics, staying at home due to a reaction) daily for 7 days following vaccination A telephone call was made to check for adverse reactions on the 3rd and 7th day after vaccination.

Between da 29 and 43 ostvaccination blood and urine sam les were taken and diar

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cards collected.

All adverse events were collected throughout the duration of the study (36 ± 7 days). If an adverse event remained unresolved at the conclusion of the study, a clinical assessment was to be made by the investigator and Medical Monitor to determine whether continued follow-up of the adverse event was warranted.

Number of subjects (planned and analyzed): It was planned to enroll approximately 90 healthy adult subjects, between 18 and 45 years of age into this study (30 in the Men ACWY group, 30 in the Men A+CWY group, 30 in the control group). Actual enrolment, both overall and into each vaccination group was exactly as planned (i.e., 30 subjects were enrolled into each vaccination group).

All subjects were included in the safety population and all safety data were included in the safety analyses. Data from all subjects were also included in at least one of the immunogenicity analyses.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria

Individuals eligible for enrolment into this study were male and female adult volunteers who were:

1) 18 to 45 years of age
2) mentally competent
3) able to give written informed consent prior to study entry
4) available for all the visits scheduled in the study
5) females with a negative pregnancy test prior to vaccination, and willing to practice adequate contraception for the duration of the trial
6) in good health as determined by:
    a. medical history
    b. screening laboratory tests
    c. physical examination
    d. clinical judgment of the investigator

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Exclusion criteria

Individuals were not to be enrolled into the study if:

1) they were unwilling or unable to give written informed consent to participate in the study
2) they had any serious disease such as:
    a. cancer (except for benign or localized skin cancer and non-metastatic prostate cancer not presently treated with chemotherapy)
    b. autoimmune disease (including rheumatoid arthritis)
    c. arteriosclerotic disease or diabetes mellitus
    d. chronic obstructive pulmonary disease (COPD)
    e. acute or progressive hepatic disease
    f. acute or progressive renal disease
    g. congestive heart failure
3) they had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component
4) they had a known or suspected impairment/alteration of immune function resulting from:
    a. receipt of immunosuppressive therapy (any cortical steroid or cancer chemotherapy),
    b. receipt of immunostimulants
    c. receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the 3 months prior to planned enrolment and throughout the study
    d. suspected or known HIV infection or HIV related disease
5) they had had laboratory confirmed N. meningitidis infection
6) they had been immunized with any polysaccharide meningococcal vaccine
7) they had received another vaccine or any investigational agent within 90 days prior to planned enrolment
8) they had experienced any acute respiratory disease or infections requiring systemic antibiotic or antiviral therapy or they had experienced fever ≥ 38°C within 3 days prior to planned enrolment

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9) they were females with positive pregnancy test
10) they had any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

Test product, dose and mode of administration, lot number:

Chiron Men ACWY vaccine was obtained by extemporaneous mixing just before injection of the contents of two vials:

Vial A, Chiron Men A l

lyophilized component:

- Men A-CRM_{197}conjugate	(b) (4) µg of oligosaccharide
- (b) (4)	(b) (4)
- Potassium dihydrogen phosphate (adj. to pH (b) (4))	

To be diluted with

Vial B

Chiron Men CWY full liquid vaccine

(b) (4) mL per each vial:

- Men C-CRM_{197} conjugate	(b) (4) µg of oligosaccharide
- MenW-CRM_{197} conjugate	(b) (4) µg of oligosaccharide
- MenY-CRM_{197} conjugate	(b) (4) µg of oligosaccharide
- Aluminum phosphate	(b) (4) mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	(b) (4)
- Sodium phosphate monobasic	(b) (4)
- Water for injection qs (b) (4) mL	

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Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197}conjugate, Men C-CRM_{197}conjugate, Men W_{135}-CRM_{197}conjugate, Men Y-CRM_{197}conjugate		

After reconstitution Chiron Men ACWY vaccine had the following composition per 0.5 mL of injectable solution:

- Men A CRM_{197}- conjugate	10 µg of oligosaccharide
- MenC CRM_{197}- conjugate	10 µg of oligosaccharide
- MenW CRM_{197}- conjugate	10 µg of oligosaccharide
- MenY-CRM_{197} conjugate	10 µg of oligosaccharide
- Aluminum phosphate	0.3 mg Al^{3+}
- Sodium chloride - (b) (4) - Sodium phosphate monobasic (pH (b) (4) - Potassium dihydrogen phosphate - (b) (4)	(b) (4)
- Water for injection qs	0.5 mL

One dose of the Chiron Men ACWY vaccine was injected IM in the deltoid region.

Chiron Men A vaccine was obtained by extemporaneous mixing just before injection of two vials:
Vial C, Chiron Men A lyophilized component:

- Men A-CRM_{197} conjugate	(b) (4) µg of oligosaccharide
- (b) (4) - Potassium dihydrogen phosphate (adj. to pH (b) (4)	(b) (4)

To be diluted with
Vial D, Solvent (b) (4) mL per each vial:

- Aluminum phosphate	(b) (4) mg Al^{3+}
- Sodium chloride - (b) (4) - Sodium phosphate monobasic	(b) (4)

Name of Sponsor/Company Chiron Vaccines	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197}conjugate, Men C-CRM_{197}conjugate, Men W_{135}-CRM_{197}conjugate, Men Y-CRM_{197}conjugate	**Study number: V59P1**	

- Water for injection qs [(b) (4)] mL

After reconstitution Chiron Men A vaccine had the following composition per 0.5 mL of injectable solution:

- Men A-CRM_{197} conjugate	10 µg of oligosaccharide
- Aluminum phosphate	0.3 mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic (pH [(b) (4)])	
- Potassium dihydrogen phosphate	
- (b) (4)	
- Water for injection qs	0.5 mL

One dose of the Chiron Men A vaccine was injected IM in the deltoid region.

Chiron Men CWY vaccine (available in one vial):

Vial E, Chiron Men CWY full liquid vaccine [(b) (4)] mL per each vial:

- MenC-CRM_{197} conjugate	[(b) (4)] µg of oligosaccharide
- MenW-CRM_{197} conjugate	[(b) (4)] µg of oligosaccharide
- MenY-CRM_{197} conjugate	[(b) (4)] µg of oligosaccharide
- Aluminum phosphate	(b) (4) mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic	
- Water for injection qs	[(b) (4)] mL

One 0.5 mL dose of the Chiron Men CWY full liquid vaccine was injected IM in the deltoid region and had the following composition per 0.5 mL of injectable solution:

- MenC CRM_{197}- conjugate	10µg of oligosaccharide
- MenW-CRM_{197} conjugate	10µg of oligosaccharide
- MenY-CRM_{197} conjugate	10µg of oligosaccharide

Name of Sponsor/Company Chiron Vaccines	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine	**Volume:** **Page:**	
Name of Active Ingredient Men A-CRM_{197}conjugate, Men C-CRM_{197}conjugate, Men W_{135}-CRM_{197}conjugate, Men Y-CRM_{197}conjugate	**Study number: V59P1**	

- Aluminum phosphate	0.3 mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic	
- Water for injection qs	0.5 mL

Duration of subject participation: 28 days (+7)

Reference vaccines, antigen content, dosage regimen, route of administration:

GSK Mencevax® (control) Meningococcal ACWY vaccine

Each dose of 0.5 mL of vaccine was obtained by extemporaneous mixing just before injection of two following vials:

Vial F

Lyophilized purified polysaccharide of N. meningitidis 200 µg, comprising:

Group A	50 µg of polysaccharide
Group C	50 µg of polysaccharide
Group W_{135}	50 µg of polysaccharide
Group Y	50 µg of polysaccharide

Vial G

Lactose	(b) (4)
NaCl	4.5 mg
Water for injection qs	up to 0.5 mL

One dose of the vaccine was injected SC in the deltoid region.

Statistical methods:

No null hypothesis was formulated for this study. Analyses were run descriptively for each vaccination rou . The sam le size was estimated to be sufficient to rovide a

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good estimate of the safety of the vaccines.

Summary and Conclusions:

Immunogenicity results

For each serogroup and in each vaccination group (Men ACWY, Men A+CWY and control) the ELISA anticapsular IgG geometric mean concentrations (GMCs, assayed by total IgG) and the SBA geometric mean titers (GMTs) measured using both rabbit and human complement (rC', hC'), increased after vaccination.

At day 29, the percentage of subjects with hC' SBA titers ≥ 1:4 for each serogroup ranged between 90% and 100% in the investigational vaccination groups and between 83% and 100% in the control group. The percentage of subjects from each vaccination group with rC' SBA titers ≥ 1:128 for each serogroup ranged between 93% and100%.

The percentage of subjects with at least a fourfold increase from baseline in rC' SBA was between 87% and 100% in the investigational vaccination groups and between 77% and 100% in the control group. The majority of subjects who did not demonstrate a fourfold increase in titers after vaccination already had high prevaccination titers.

In general, immune responses were similar among vaccination groups. However, the immune response to serogroup A when measured with rC' SBA appeared higher for the control group (although this difference did not attain statistical significance). In contrast, when the same sera were analyzed in an assay which used hC', the response for serogroup A was higher for the group receiving the investigational Men ACWY vaccine. This latter assay also indicated a trend for a higher immune response to serogroup W for those who received the conjugate vaccine.

Safety results

The vaccines were safe and well tolerated in the 90 healthy adults of this study.

No unexpected adverse reactions occurred during the study. No vaccine-related serious

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adverse events were reported.

No significant abnormal changes in laboratory parameters occurred during this study.

The most frequent local reaction reported was pain at the injection site (43%, 40% and 47% of the Men ACWY, Men A+CWY and control groups, respectively). Only one subject (a recipient of the control), reported severe pain. The most frequent systemic reactions were headache (17%, 13% and 20% of the Men ACWY, Men A+CWY and control groups, respectively) and chills (13% of all vaccination groups). With the exception of severe malaise in one Men ACWY recipient, severe chills in two Men ACWY recipients, and severe headache in one subject from each vaccination group, all local and systemic reactions were either mild or moderate in severity. All local and systemic reactions resolved within 7 days.

Two subjects reported an axillary temperature between 38°C and 39°C on day 4; one in the Men ACWY and one in the Men A+CWY vaccination group. No subject experienced axillary temperature >39°C during the study.

In addition to the local and systemic reactions reported during the 7 days immediately following vaccination, five other adverse events were reported during the study, four classified as mild in severity and one as moderate in severity. Three of these other adverse events were assessed as at least possibly related to a study vaccine. One subject in the ACWY group experienced somnolence , one subject in the control group reported paresthesia, and another subject in the control group reported lymphadenopathy. These adverse events were transient (lasting no more than 7 days) and mild in severity.

Conclusions

The results of this phase I study of a tetravalent meningococcal ACWY vaccine conjugated to CRM_{197} indicate that a single dose containing 10µg of each antigen is safe and well tolerated in this population of healthy adults aged 18-45 years.

All four antigens were immunogenic (when assessed both by ELISA and SBA) and immune responses were comparable among vaccination groups, as expected for these vaccines (polysaccharide and primary conjugate) in adults.

Name of Sponsor/Company Chiron Vaccines	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine	**Volume:** **Page:**	
Name of Active Ingredient Men A-CRM_{197}conjugate, Men C-CRM_{197}conjugate, Men W_{135}-CRM_{197}conjugate, Men Y-CRM_{197}conjugate	**Study number: V59P1**	
It has been previously shown that the advantage in terms of immunogenicity and immunological memory of conjugate vaccines over plain polysaccharide vaccines is greatest in younger age groups. Therefore these preliminary results in adults support further clinical investigation in a pediatric population.		

rC' SBA GMTs and GMRs

Sero-group	Study day	Men ACWY N=30	Men A+CWY N=30	Control N=30
A	Day 1 (95% CI)	7.88 (3.77 – 16)	8.09 (3.87 – 17)	5.29 (2.53 – 11)
	Day 29 (95% CI)	989 (558 – 1754)	2566 (1448 – 4549)	3132 (1767 – 5552)
	Day 29/Day 1 (95% CI)	126 (54- 294)	317 (135-743)	592 (253-1386)
C	Day 1 (95% CI)	4.8[a] (2.42 – 9.54)	5.04 (2.57 - 9.9)	6.24 (3.18 – 12)
	Day 29 (95% CI)	4480[a] (2455 – 8176)	3794 (2100 – 6855)	3829 (2119 – 6918)
	Day 29/Day 1 (95% CI)	933 (410-2121)	753 (336-1689)	614 (274-1376)
W	Day 1 (95% CI)	35 (13 – 91)	19 (7.31 – 50)	25 (9.72 – 66)
	Day 29 (95% CI)	10343 (5988 – 17865)	10376 (6007 – 17923)	6795 (3934 – 11737)
	Day 29/Day 1 (95% CI)	297 (118-745)	543 (216-1362)	268 (107-671)
Y	Day 1 (95% CI)	298 (130 – 682)	448 (196 – 1024)	796 (348 – 1822)
	Day 29 (95% CI)	22075 (14689 – 33175)	24034 (15993 – 36120)	14630 (9735 - 21987)
	Day 29/Day 1 (95% CI)	74 (32-174)	54 (23-126)	18 (7.84-43)

[a]N = 29 subjects

Percentage of Subjects With rC' SBA ≥ 1:4, ≥ 1:8, and ≥ 1:128 Before and After Vaccination

Sero-group	Threshold	Study day	Men ACWY % (95% CI) N=30		Men A+CWY % (95% CI) N=30		Control % (95% CI) N=30	
A	≥ 1:4	Day 1	37	(20 – 56)	33	(17 - 53)	27	(12 - 46)
		Day 29	97	(83 - 100)	97	(83 - 100)	100	(88 - 100)
	≥ 1:8	Day 1	37	(20 – 56)	33	(17 - 53)	27	(12 – 46)
		Day 29	97	(83 - 100)	97	(83 - 100)	100	(88 – 100)
	≥ 1:128	Day 1	17	(6 – 35)	23	(10 - 42)	13	(4 - 31)
		Day 29	93	(78 – 99)	97	(83 - 100)	100	(88 - 100)
C	≥ 1:4	Day 1	24 [a]	(10 – 44)	23	(10 - 42)	37	(20-56)
		Day 29	100 [a]	(88 - 100)	100	(88 - 100)	100	(88 - 100)
	≥ 1:8	Day 1	24 [a]	(10 – 44)	23	(10 – 42)	33	(17 - 53)
		Day 29	100 [a]	(88 - 100)	100	(88 - 100)	100	(88 - 100)
	≥ 1:128	Day 1	7 [a]	(1 – 23)	7	(1 - 22)	10	(2 - 27)
		Day 29	97 [a]	(82 - 100)	100	(88 - 100)	93	(78 - 99)
W	≥ 1:4	Day 1	67	(47 – 83)	43	(25 - 63)	47	(28 - 66)
		Day 29	100	(88 - 100)	100	(88 - 100)	100	(88 - 100)
	≥ 1:8	Day 1	63	(44 – 80)	43	(25 - 63)	47	(28 - 66)
		Day 29	100	(88 - 100)	100	(88 - 100)	100	(88 - 100)
	≥ 1:128	Day 1	33	(17 – 53)	30	(15 - 49)	43	(25 - 63)
		Day 29	100	(88 - 100)	100	(88 - 100)	100	(88 - 100)
Y	≥ 1:4	Day 1	83	(65 – 94)	90	(73 - 98)	93	(78 - 99)
		Day 29	100	(88 - 100)	100	(88 - 100)	100	(88 - 100)
	≥ 1:8	Day 1	83	(65 – 94)	90	(73 - 98)	93	(78 – 99)
		Day 29	100	(88 - 100)	100	(88 - 100)	100	(88 – 100)
	≥ 1:128	Day 1	77	(58 - 90)	87	(69 - 96)	90	(73 – 98)
		Day 29	100	(88 – 100)	100	(88 - 100)	100	(88 – 100)

Percentage of Subjects With at Least a Fourfold Increase of rC' SBA.

Sero-group	Men ACWY N=30 %	Men A+CWY N=30 %	Control N=30
A	87 (69 – 96)	87 (69 - 96)	97 (83 -100)
C	97[a](82 - 100)	97 (83 - 100)	100 (88 - 100)
W	100 (88 - 100)	97 (83 - 100)	100 (88 - 100)
Y	93 (78 – 99)	87 (69- 96)	77 (58- 90)

[a]N = 29 subjects

ELISA GMCs (total IgG: µg/mL) Before and After Vaccination

Sero-group	Study Days	Men ACWY N=30	Men A+CWY N=30	Control N=30
A	Day 1 (95% CI)	5.2 (3.15 - 8.56)	6.04 (3.67 - 9.96)	3.93 (2.39 - 6.48)
	Day 29 (95% CI)	30 (20 – 46)	37 (24 – 57)	35 (23 – 53)
	Day 29/Day 1 (95% CI)	5.81 (3.79-8.89)	6.17 (4.03-9.45)	8.82 (5.76-14)
C	Day 1 (95% CI)	0.45 (0.23 - 0.9)	0.23 (0.12 - 0.46)	0.28 (0.14 - 0.55)
	Day 29 (95% CI)	22 (14 – 35)	14 (9.03 – 23)	27 (17 – 44)
	Day 29/Day 1 (95% CI)	48 (24-94)	62 (31-121)	100 (51-195)
W	Day 1 (95% CI)	0.44 (0.24 - 0.8)	0.27 (0.15 - 0.48)	0.6 (0.33 - 1.09)
	Day 29 (95% CI)	36 (22 – 60)	28 (17 – 47)	24 (14 – 39)
	Day 29/Day 1 (95% CI)	82 (47-142)	107 (62-185)	39 (22-68)
Y	Day 1 (95% CI)	0.72 (0.38 - 1.36)	0.67 (0.35 - 1.27)	1.19 (0.63 - 2.26)
	Day 29 (95% CI)	50 (33 – 76)	51 (33 – 77)	55 (36 – 84)
	Day 29/Day 1 (95% CI)	69 (39-123)	76 (43-135)	46 (26- 82)

GMCs (high avidity ELISA, µg/mL) Before and After Vaccination

Sero-group	Study Day	Men ACWY N=30	Men A+CWY N=30	Control N=30
A	Day 1 (95% CI)	0.67 (0.36-1.24)	0.85 (0.46-1.58)	0.45 (0.24-0.83)
	Day 29 (95% CI)	10 (6.6-16)	14 (8.86-22)	9.82 (6.24-15)
	Day 29/Day 1 (95% CI)	16 (9.28-26)	16 (9.79-27)	22 (13-37)
C	Day 1 (95% CI)	0.21 (0.13-0.34)	0.13 (0.079-0.2)	0.16 (0.1-0.25)
	Day 29 (95% CI)	7.72 (4.74-13)	5.2 (3.19-8.46)	8.5 (5.22-14)
	Day 29/Day 1 (95% CI)	37 (20-66)	42 (23-76)	54 (29-97)
W	Day 1 (95% CI)	0.21 (0.13 – 0.33)	0.2 (0.13 - 0.32)	0.29 (0.19 – 0.46)
	Day 29 (95% CI)	12 (6.54-21)	9.91 (5.55-18)	6.74 (3.77-12)
	Day 29/Day 1 (95% CI) (95% CI)	55 (32-94)	49 (29-84)	23 (13-39)
Y	Day 1 (95% CI)	0.35 (0.21-0.58)	0.31 (0.19-0.52)	0.57 (0.34-0.95)
	Day 29 (95% CI)	18 (12-29)	21 (13-33)	20 (12-31)
	Day 29/Day 1 (95% CI)	52 (32-87)	67 (41-111)	34 (21-57)

2-6 hC' SBA GMTs and GMR

Sero-group	Study Day	Men ACWY N=30	Men A+CWY N=30	Control N=30
A	Day 1 (95% CI)	3.79 (2.71 – 5.28)	3.7 (2.65-5.16)	2.73 (1.95-3.8)
	Day 29 (95% CI)	42 (23 – 76)	66 (36 – 119)	28 (15 – 50)
	Day 29/Day 1 (95% CI)	11 (6.31-20)	18 (10-31)	10 (5.73-18)
C	Day 1 (95% CI)	9.83 (5.89 – 16)	7.71 (4.62 – 13)	6.61 (3.96 – 11)
	Day 29 (95% CI)	213 (106 – 427)	162 (80 – 325)	223 (111 – 448)
	Day 29/Day 1 (95% CI)	22 (11-41)	21 (11-40)	34 (18-64)
W	Day 1 (95% CI)	20 (11 – 36)	14 (7.9 – 25)	23 (13 – 40)
	Day 29 (95% CI)	248 (123 – 500)	142 (71 – 287)	99 (49 – 199)
	Day 29/Day 1 (95% CI)	12 (6.35-24)	10 (5.24-20)	4.38 (2.27-8.45)
Y	Day 1 (95% CI)	7.15 (4.43-12)	7.54 (4.67-12)	13 (8.2-21)
	Day 29 (95% CI)	263 (151-457)	338 (194-588)	198 (114-344)
	Day 29/Day 1 (95% CI)	37 (21-66)	45 (25-80)	15 (8.36-27)

Percentage of Subjects With hC' SBA titer ≥ 1:4 and ≥ 1:8 Before and After Vaccination.

Serogroup	Threshold	Study day	Men ACWY % (95% CI) N=30	Men A+CWY % (95% CI) N=30	Control % (95% CI) N=30
A	≥ 1:4	Day 1	40 (23– 59)	33 (17 – 53)	20 (8 – 39)
		Day 29	90 (73 – 98)	97 (83 - 100)	83 (65 - 94)
	≥ 1:8	Day 1	20 (8-39)	20 (8-39)	10 (2 - 27)
		Day 29	77 (58-90)	87 (69-96)	80 (61 – 92)
C	≥ 1:4	Day 1	63 (44 - 80)	60 (41 - 77)	57 (37 - 75)
		Day 29	100 (88 - 100)	100 (88 - 100)	100 (88 - 100)
	≥ 1:8	Day 1	60 (41-77)	50 (31-69)	47 (28 - 66)
		Day 29	97 (83-100)	97 (83-100)	100 (88 – 100)
W	≥ 1:4	Day 1	77 (58 - 90)	67 (47 - 83)	77 (58 – 90)
		Day 29	100 (88 - 100)	93 (78 - 99)	97 (83 - 100)
	≥ 1:8	Day 1	77 (58 - 90)	63 (44 – 80)	77 (58 –90)
		Day 29	100 (88 – 100)	93 (78 – 99)	97 (83 - 100)
Y	≥ 1:4	Day 1	50 (31-69)	63 (44-80)	83 (65-94)
		Day 29	100 (88-100)	100 (88-100)	100 (88-100)
	≥ 1:8	Day 1	43 (25-63)	57 (37 - 75)	70 (51 – 85)
		29	100 (88-100)	100 (88-100)	100 (88 – 100)

Local Reactogenicity Within 7 Days Following Vaccination

	Men ACWY		**[a]Men A+CWY**				**Control**	
	N = 30		N = 30				N = 30	
Local reactions	All	Severe	All	Severe			All	Severe
Ecchymosis	0	0	0	0			0	0
Erythema	1 (3%)	0	0	0			0	0
Induration	4 (13%)	0	3 (10%)	0			1 (3%)	0
Swelling	0	0	1 (3%)	0			0	0
Pain	13 (43%)	0	16 (53%)	0			14 (47%)	1 (3%)

[a]No difference in the frequency of each local reaction was observed between the injection sites of the Men A and Men CWY vaccines (Appendix 16.1.9.6).

Systemic Reactogenicity Within 7 Days Following Vaccination

	Men ACWY		**Men A+CWY**		**Control**		**Vaccine group difference**
Systemic reactions	N = 30		N = 30		N = 30		P-value
	All	Severe	All	Severe	All	Severe	
Malaise	3 (10%)	1 (3%)	1 (3%)	0	1 (3%)	0	.43
Chills	4 (13%)	2 (7%)	4 (13%)	0	4 (13%)	0	1.0
Headache	5 (17%)	1 (3%)	4 (13%)	1 (3%)	6 (20%)	1 (3%)	.79
Nausea	2 (7%)	0	0	0	3 (10%)	0	.23
Myalgia	3 (10%)	0	2 (7%)	0	2 (7%)	0	.86
Arthralgia	0	0	1 (3%)	0	1 (3%)	0	.60

Systemic Reactogenicity Within 7 Days Following Vaccination

	Men ACWY	**Men A+CWY**	**Control**	**Vaccination group differences**
	N = 30	N = 30	N = 30	P-value
Other				
Axillary Temperature ≥ 38 °C	1 (3%)	1 (3%)	0	.60
Stayed Home Due to Reaction	1 (3%)	1 (3%)	0	.61
Analgesic Antipyretic Medication Used	3 (10%)	0	2 (7%)	.23

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		
Title of study: A Phase II, Open Label, Single Center, Controlled Study to Evaluate the Anamnestic Response of Healthy Adults Previously Vaccinated With Either Chiron Meningococcal ACWY Conjugate Vaccine or GSK Mencevax® After Challenge With a Reduced Dose of a Licensed Polysaccharide Meningococcal ACWY Vaccine.		
Protocol number: V59P1E1		
Investigator: Silvio Crestani, MD, Institute for Pharmacokinetic and Analytical Studies, Via Mastri 36, CH 6853 Ligornetto, Switzerland.		
Study center: Institute for Pharmacokinetic and Analytical Studies, Via Mastri 36, CH 6853 Ligornetto, Switzerland.		
Publication (reference): none		
Study period: **(date of first enrolment)** 20 NOV 03 **(date of last completed)** 18 DEC 03	**Phase of development:** Phase II	

Objectives:

Immunogenicity Objectives

- To evaluate serum antibody responses to *N meningitidis* serogroups ACWY 28 days following administration of a reduced dose of a meningococcal ACWY polysaccharide (PS) vaccine (PS-ACWY) vaccine at least 1 year after vaccination with Novartis MenACWYACWY or GlaxoSmithKline (GSK) Mencevax vaccine (control).
- To evaluate the persistence of serum antibodies to *N meningitidis* serogroups ACWY at least 1 year after vaccination with either Novartis MenACWYACWY or GSK Mencevax vaccine.
- To evaluate serum antibody responses to *N meningitidis* serogroups ACWY 7 days following administration of a reduced dose of a PS-ACWY vaccine at least 1 year

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

after vaccination with Novartis MenACWY or GSK Mencevax vaccine.

- To assess the kinetics of plasma cell and memory B-cell generation following administration of a reduced dose of a PS-ACWY vaccine at least 1 year after vaccination with Novartis MenACWY or GSK Mencevax vaccine.

Safety Objectives

- To monitor the safety of a reduced dose of a licensed PS-ACWY vaccine in all study subjects.

Methodology:

Approximately 30 healthy adult subjects who had previously participated in Novartis study V59P1 were to be enrolled into this study, according to the following two groups. Subjects were to be selected according to an enrolment list provided by Novartis Biostatistics and Clinical Data Management (BCDM).

Group A (ACWY group):

Approximately 15 healthy adult subjects previously vaccinated with Novartis MenACWY were to receive a reduced dose of a licensed PS-ACWY vaccine (the normal dose contains 50 µg of each of the four polysaccharide antigens, the reduced dose administered in this study consisted of 5 µg of each ACWY polysaccharide antigens).

Group B (control group):

Approximately 15 healthy adult subjects previously vaccinated with GSK Mencevax vaccine were to receive a reduced dose of a licensed PS-ACWY vaccine. Subjects were to be screened to ensure they were in good health and met all inclusion criteria and no exclusion criteria. Medical history was to be obtained and a physical examination was to be performed.

On day 1 a blood sample was to be taken before the administration of PS-ACWY, for the evaluation of persistence of antibodies at least 1 year after vaccination. A reduced dose of PS-ACWY was to be administered intramuscularly (IM) in the deltoid region. Subjects were to remain in the clinic for 60 minutes after study injection to monitor for any hypersensitivity reactions and other adverse events (AEs).

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Subjects were to be monitored for safety for the duration of the study. The subjects were instructed to complete Diary Cards to describe local reactions (i.e., erythema, induration, swelling, and pain), systemic reactions (i.e., malaise, chills, headache, nausea, myalgia, and arthralgia), other indicators of reactogenicity (such as if subject stayed home due to reaction, if subject used analgesics/antipyretics) and other AEs, and to record axillary temperature measurements, daily for 7 days following PS-ACWY administration (days 1 to 7). A telephone call checked for subjects' health status on the third day after PS-ACWY administration.

Serious adverse events (SAEs) and AEs requiring a physician visit or leading to subject withdrawal were to be collected throughout the study and monitored until they were resolved. If an AE remained unresolved at the conclusion of the study, a clinical assessment was to be made by the investigator and medical monitor to determine whether continued follow-up of the AE was warranted.

On day 8 all subjects were to return to the clinic for a blood sample for immunogenicity analyses. At the final study visit (day 29), blood and urine samples were to be collected from all subjects.

V59P1 Primary Vaccination Received	**V59P1E1 Challenge with a reduced dose of licensed PS-ACWY vaccine (GSK Mencevax)**					
	Screening Visit [a]	**day 1[b]**	**day 6[c]**	**day 8[d]**	**day 15[e]**	**day 29[f]**
Novartis MenACWY **GSK Mencevax**	Informed Consent Blood sample Urine sample	Blood sample Diary Card dispensed PS-ACWY administration	Blood sample	Diary Card collection Blood sample	Blood sample	Blood sample Urine sample

a < 13 days prior to day 1
b > 360 days after primary vaccination with either GSK Mencevax or Novartis MenACWY
c 5 days after study dose administration
d 7 days after study dose administration
e 14 days after study dose administration
f 28 days after study dose administration
Note: a telephone call was also made to the subjects on the 3rd day after administration.

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A subset of subjects were to provide an extra blood sample at all study visits and were also to return to the clinic on day 6 and day 15 for an additional blood sample collection. Additional immunogenicity analyses were to be carried out on these samples relating to the kinetics of plasma cell and memory B-cell generation in response to the reduced vaccine dose administration.

In samples drawn on each of these study days, the number of plasma cells secreting immunoglobulin G (IgG) and specific antibodies were to be measured by enzyme-linked immunospot assay (ELISPOT) on freshly isolated mononuclear cells.

The frequency of antigen-specific B cells was to be measured using a (b) (4)
(b) (4)
(b) (4)

Number of subjects (planned and analyzed):

Approximately 30 healthy adult subjects who had previously participated in Novartis study V59P1 and who had received either Novartis MenACWY or GSK Mencevax were to be enrolled in this study. Subjects who provided only a blood sample prior to administration of the study vaccine were to be included in the immunogenicity analyses to evaluate the persistence of antibodies to *N meningitidis* serogroups ACWY. Subjects who provided a blood sample prior to vaccination and on day 29 and/or day 8 were to be included in the immunogenicity analyses to evaluate the persistence of antibodies and the anamnestic response to *N meningitidis* serogroups ACWY. A subset of subjects who provided a blood sample on study days 1, 6, 8, 15, and 29 were to be included in the analysis to evaluate the kinetics of plasma cell and memory B-cell generation. In total 29 subjects were enrolled in the study, of these 15 had received Novartis MenACWY and 14 had received GSK Mencevax vaccine in the V59P1 study.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria

Individuals eligible for enrolment into this study were male and female adult volunteers previously participating in V59P1 study who were:

1. Mentally competent.
2. Able to give written informed consent prior to study entry.

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3. Available for all the visits scheduled in the study.
4. Females with a negative pregnancy test prior to study dose administration and willing to practice adequate contraception for the duration of the trial.
5. In good health as determined by:
   - Medical history,
   - Screening laboratory tests,
   - Physical examination,
   - Clinical judgment of the investigator.

Exclusion Criteria

Individuals were not to be enrolled into the study if:

1. They were unwilling or unable to give written informed consent to participate in the study.
2. They had any serious disease such as:
   - Cancer,
   - Autoimmune disease,
   - Arteriosclerotic disease or diabetes mellitus,
   - Chronic obstructive pulmonary disease,
   - Acute or progressive hepatic disease,
   - Acute or progressive renal disease,
   - Congestive heart failure.
3. They had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component.
4. They had a known or suspected impairment/alteration of immune function resulting from:
   - Receipt of immunosuppressive therapy;
   - Receipt of immunostimulants;
   - Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the past 3 months and for the full length of the study;

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- Suspected or known human immunodeficiency virus (HIV) infection or HIV related disease.

5. They had not received either Novartis MenACWY or GSK Mencevax in V59P1.
6. They had had laboratory confirmed *N meningitidis* infection.
7. They had received another vaccine or any investigational agent within the 90 days prior to vaccination.
8. They had experienced any acute respiratory disease or infections requiring systemic antibiotic or antiviral therapy or they had experienced fever ≥ 38°C within the 3 days prior to vaccination.
9. They were females with a positive pregnancy test and/or females who were breastfeeding.
10. They had received systemic antibiotic therapy within 21 days prior to vaccination.
11. They had any condition that, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

Test product, dose, mode of administration, lot number:

One injection with a reduced dose of the licensed tetravalent meningococcal ACWY polysaccharide vaccine (GSK Mencevax) was to be administered IM in the deltoid region. The licensed vaccine contains 50 µg of plain polysaccharide from each of four meningococcal serogroups (A, C, W135, and Y) in a single 0.5 mL dose. The 0.5 mL dose administered for this study was to be diluted from the standard dose and thus contained approximately 5 µg of polysaccharide antigen from each of the four component serogroups.

Lot number: N402A47A

Expiry date: 10-2004

Duration of study:

Approximately 6 weeks overall: 2 weeks of enrollment and 4 weeks of individual subject participation.

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Reference therapy, dose, mode of administration, lot number:
No reference vaccines were to be administered.

Criteria for evaluation:
Immunogenicity
The immune response to a reduced dose of a licensed PS-ACWY vaccine in subjects previously vaccinated with Novartis **Men**ACWY or GSK Mencevax for all four serogroups were assessed in terms of:

- Serum bactericidal assay (SBA) geometric mean titer (GMT) increase at 7 and 28 days after vaccination as compared to baseline values (day 1).
- Percentage of subjects with SBA titer ≥1: 4 before (day 1), 7, and 28 days after vaccination.
- Enzyme-linked immunosorbent assay (ELISA) geometric mean concentration (GMC) before (day 1), 7, and 28 days after vaccination.
- Proportion of subjects in each study group who exhibit at least a 4-fold increase in SBA titer from baseline for each of the meningococcal serogroups (A, C, W, Y) as measured 7 and 28 days after vaccination.
- Proportion of subjects in each study group who exhibit at least a 4-fold increase in specific antibody concentration, measured by ELISA, from baseline for each of the meningococcal serogroups (A, C, W, Y) as measured 7 and 28 days after vaccination.
- The results of the assessment, by ELISPOT assay and the polyclonal stimulation of B cells, of the kinetics of plasma cell and memory B-cell generation and its correlation to specific serum antibody levels will be based on the frequency of those cells at days 1, 6, 8, 15, and 29.

Safety
Measures of safety included data from physical examination, reports of local (i.e., erythema, induration, swelling, and pain) and systemic (i.e., malaise, chills, headache, nausea, myalgia, and arthralgia) reactions as well as reports of axillary temperature, of whether the subject stayed home due to reaction and the use of analgesics/ antipyretics within 7 days from the vaccination. All other AEs occurring up to day 7 in addition to SAEs and/or AEs requiring a physician visit and/or resulting in premature withdrawal

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from the study were collected throughout the study.

Statistical methods:

There was no prespecified statistical test related to the objectives. All analyses were run descriptively.

Statistical power considerations:

Assuming 30 evaluable subjects (15 subjects in each of the two vaccine groups) there was a 85% power to detect a 7-fold increase in SBA GMTs (a difference of $\log_{10}(7)=0.845$ in the $\log_{10}$ SBA geometric mean titers) at 28 days after administration of a reduced dose of PS-ACWY.

The power calculation was based on a two-sided, t-test comparing two means using a 5% level of significance and assuming a common standard deviation of the $\log_{10}$ (SBA GMTs) = 0.74. The standard deviation estimate was based on a previous work by Granoff, which suggested that the standard deviation σ of titers (SBA titers for Men C 1 month after administration of a reduced dose of PS-ACWY) is approximately 0.57 on the $\log_{10}$ scale (degree of freedom = 17, 80% CI of σ: 0.47 to 0.74). The power calculations are not adjusted for multiple statistical tests performed for the four serogroups.

Summary and Conclusions:

Immunogenicity results

At baseline, antibody titers in subjects primed with MenACWY and with Mencevax were similar as determined by human complement serum bactericidal assay (hSBA) GMTs and by the percentage of subjects with a titer of greater than or equal to 1:4 or 1:8. The immune response in subjects primed with MenACWY, as measured by hSBA GMTs, increased (1.45- to 2.15-fold above baseline) on day 8 after challenge against each of the four meningococcal antigens but the challenge with a reduced dose of PS-ACWY did not induce hSBA GMT increases in subjects primed with Mencevax. Antibody titers continued to increase in the MenACWY-primed subjects as evidenced by day 29 titers (2.04- to 2.79-fold above baseline) while no immune response was observed in the Mencevax subjects. By day 29 after challenge, the titers against A, C, and Y serogroups were statistically significantly greater in MenACWY-primed subjects than in Mencevax-primed subjects ($P < .05$). Baseline hSBA titers were high for the MenACWY group (range 53% to 100%) and the control group (range 64% to 100%) for

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each of the four meningococcal serogroups analyzed. Following challenge, no major increases in the percentage of Mencevax recipients with a titer of at least 1:8 was observed while all MenACWY subjects had attained this threshold by day 8 against serogroups C, W, and Y, and 73% of MenACWY subjects attained this threshold by day 29 for serogroup A. Following challenge, no Mencevax subjects attained a 4-fold rise in hSBA titers against the four meningococcal serogroups. A few MenACWY subjects attained this threshold by day 8 (7% for both A and W, 20% for both C and Y) and slightly more subjects attained this threshold by day 29 (20% A, 13% W, 27% for both C and Y). No subjects in the trial attained a 4-fold rise in ELISA titers against the four serogroups by day 8, and by day 29 only a few MenACWY subjects (7%) attained this threshold against the A and C serogroups. The challenge did not induce ELISA GMC increases in subjects primed with Mencevax while antibody titers only slightly increased in the MenACWY primed subjects.

Safety results

Overall reactogenicity to the polysaccharide vaccine was low and both study groups showed the same reactogenicity profile. The percentages of subjects experiencing each local and systemic reaction were similar between subjects previously vaccinated with either MenACWY or Mencevax. With the exception of injection-site pain (60% MenACWY group, 43% Mencevax), the percentage of subjects experiencing other local reactions ranged from 0% to 7% in both groups. The most frequent systemic reactions were myalgia (27% MenACWY group, 14% Mencevax), headache (20% MenACWY group, 29% Mencevax group), and malaise (20% MenACWY group, 0% Mencevax group). The percentage of subjects experiencing other systemic reactions ranged from 0% to 14% in both groups. No severe reactions were reported and all local and systemic reactions were transient. Only one AE was reported during the study and it was judged by the investigator to be not related to the study vaccine. No SAEs, possibly- or probably-related AEs, AEs leading to subject withdrawal from study, or deaths were reported during the study.

Conclusions

The results of this study demonstrated an anamnestic immune response against all four A, C, W, Y meningococcal serogroups in healthy adult subjects previously vaccinated with MenACWY but not for subjects who received Mencevax in the V59P1 study. For the former group both hSBA GMTs and the percentage of subjects with titers greater or

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equal to 1:4 increased following the administration of a reduced dose of PS-ACWY (i.e., 5 µg of each A, C, W, Y polysaccharide antigen), while for the control group both immunogenicity indicators remained essentially similar to baseline values. Baseline hSBA titers were similar between the MenACWY and Mencevax groups and the percentages of hSBA titers > 1:4 were high for the MenACWY group (range 53% to 100%) and the control group (range 64% to 100%) for each of the four meningococcal serogroups analyzed, demonstrating persistence of antibodies at 1 year after primary vaccination. Both baseline hSBA titers and response to challenge vaccination were lower for serogroup A compared with those determined for serogroups C, W, and Y, irrespectively of whether subjects received MenACWY or Mencevax in V59P1. Persistence of the immune response was also demonstrated using ELISA. ELISA GMCs were higher for all four meningococcal serogroups than those measured at primary vaccination (V59P1) for all subjects irrespective of administered vaccine. The reduced dose of PS-ACWY was well tolerated. The reactogenicity to the challenge was very low and similar for subjects previously vaccinated with MenACWY or with Mencevax. No SAEs, possibly- or probably-related AEs related to the vaccination, other significant AEs, AEs leading to subject withdrawal from the study, or deaths were reported during the study.

Table 2.1-1 Time and Events

STUDY VISIT	Screening	3	Phone Call[a]	3.A[b]	4	4.A[b]	5
STUDY DAY NUMBER	Up to 14 days prior to Visit 3	1	3	6	8	15	29 to 36[c]
Obtain Informed Consent	X						
Medical History	X	X					
Complete Physical Examination	X	X					X
Check Injection Site					X		X
Screen for Admission Criteria	X	X					
Follow-up Telephone Call			X				
Blood Draw for Assays	X	X		X	X	X	X
Urine sample for Assays	X						X
Measure Axillary Temperature		X					
Vaccine Administration		X					
Injection-site Examination		X		X	X	X	X
Assess Local/Systemic Reactions		X	X	X	X		
Assess Concomitant Medications	X	X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X
Diary Card Review[d]					X		X[e]
Complete Study Termination							X

a The telephone call must have been completed on day 3
b Subset only
c Window did not apply to Subset
d Review of the Diary Card and its reconciliation with the data on the Local and Systemic Reaction CRF, collected at the day 3 telephone call.
e Collection of the Diary Card
Note: All Subjects in the subset should have completed all study visits on the same days as each other.

Table 2.1-2 hSBA GMTs and GMRs

Serogroup	Study Day	hSBA GMT and GMR N (95% CI)		
		ACWY Group	Control Group	ACWY Group vs. Control Group
		N=15	N=14	*P*-value
A	Day 1	10 (4.02-25)	9.73 (3.78-25)	.97
	Day 8	14 (6.15-34)	10 (4.14-24)	.55
	Day 29	21 (9.02-50)	11 (4.48-26)	.27
	Day 8/Day 1	1.45 (1.13-1.85)	1.03 (0.8-1.33)	.059
	Day 29/Day 1	2.12 (1.49-3.03)	1.12 (0.77-1.62)	.016*
C	Day 1	87 (25-301)	62 (17-225)	.70
	Day 8	174 (56-538)	66 (20-212)	.23
	Day 29	208 (66-656)	66 (20-218)	.17
	Day 8/Day 1	2 (1.51-2.63)	1.06 (0.79-1.41)	.003**
	Day 29/Day 1	2.39 (1.74-3.29)	1.07 (0.77-1.48)	.001**
W	Day 1	170 (59-487)	114 (38-338)	.59
	Day 8	293 (119-717)	141 (56-357)	.26
	Day 29	347 (138-873)	132 (51-344)	.15
	Day 8/Day 1	1.72 (1.08-2.75)	1.24 (0.77-2.02)	.33
	Day 29/Day 1	2.04 (1.28-3.25)	1.17 (0.72-1.89)	.096
Y	Day 1	68 (31-151)	70 (31-160)	.96
	Day 8	146 (72-297)	72 (35-149)	.16
	Day 29	190 (94-386)	70 (34-146)	.055
	Day 8/Day 1	2.15 (1.56-2.95)	1.02 (0.74-1.42)	.003**
	Day 29/Day 1	2.79 (1.89-4.11)	1 (0.67-1.5)	< .001***

Source: Table 14.2.1.4, Table 14.2.1.4.1
*$P <$ .05, ** $P <$ .01, *** $P <$ .001

Table 2.1-3 Subjects With hSBA Titers ≥ 1:4

Serogroup	Study Day	Percentage (95% CI)	
		ACWY Group	Control Group
		N=15	N=14
A	Day 1	53% (27%-79%)	64% (35%-87%)
	Day 8	73% (45%-92%)	64% (35%-87%)
	Day 29	80% (52%-96%)	64% (35%-87%)
C	Day 1	100% (78%-100%)	86% (57%-98%)
	Day 8	100% (78%-100%)	93% (66%-100%)
	Day 29	100% (78%-100%)	86% (57%-98%)
W	Day 1	93% (68%-100%)	93% (66%-100%)
	Day 8	100% (78%-100%)	93% (66%-100%)
	Day 29	100% (78%-100%)	93% (66%-100%)
Y	Day 1	100% (78%-100%)	100% (77%-100%)
	Day 8	100% (78%-100%)	100% (77%-100%)
	Day 29	100% (78%-100%)	100% (77%-100%)

Source: Table 14.2.1.1

Table 2.1-4 Subjects With hSBA Titers ≥ 1:8

Serogroup	Study Day	Percentage (95% CI)	
		ACWY Group	Control Group
		N=15	N=14
A	Day 1	47% (21%-73%)	50% (23%-77%)
	Day 8	60% (32%-84%)	57% (29%-82%)
	Day 29	73% (45%-92%)	64% (35%-87%)
C	Day 1	100% (78%-100%)	71% (42%-92%)
	Day 8	100% (78%-100%)	71% (42%-92%)
	Day 29	100% (78%-100%)	79% (49%-95%)
W	Day 1	93% (68%-100%)	93% (66%-100%)
	Day 8	100% (78%-100%)	93% (66%-100%)
	Day 29	100% (78%-100%)	93% (66%-100%)
Y	Day 1	100% (78%-100%)	100% (77%-100%)
	Day 8	100% (78%-100%)	100% (77%-100%)
	Day 29	100% (78%-100%)	100% (77%-100%)

Source: Table 14.2.1.2

Table 2.1-5 ELISA GMCs and GMRs

Serogroup	Study Day	ELISA GMT and GMR N (95% CI)	
		ACWY Group	Control Group
		N=15	N=14
A	Day 1	12 (7-22)	41 (23-74)
	Day 8	13 (7.97-22)	42 (25-73)
	Day 29	18 (11-30)	40 (24-68)
	Day 8/Day 1	1.08 (0.94-1.25)	1.04 (0.9-1.21)
	Day 29/Day 1	1.45 (1.23-1.71)	0.98 (0.83-1.16)
C	Day 1	8.7 (4.28-18)	16 (7.81-34)
	Day 8	9.91 (5.07-19)	16 (7.92-32)
	Day 29	12 (6.32-23)	17 (8.78-33)
	Day 8/Day 1	1.14 (0.98-1.33)	0.98 (0.83-1.15)
	Day 29/Day 1	1.38 (1.12-1.7)	1.05 (0.84-1.3)
W	Day 1	14 (6.55-31)	21 (9.53-47)
	Day 8	16 (7.16-34)	19 (8.66-43)
	Day 29	19 (8.33-41)	19 (8.25-43)
	Day 8/Day 1	1.1 (0.98-1.23)	0.91 (0.81-1.02)
	Day 29/Day 1	1.31 (1.13-1.52)	0.89 (0.76-1.04)
Y	Day 1	24 (14-39)	53 (31-88)
	Day 8	26 (16-43)	56 (33-94)
	Day 29	31 (19-50)	57 (34-93)
	Day 8/Day 1	1.09 (0.95-1.24)	1.06 (0.92-1.21)
	Day 29/Day 1	1.31 (1.11-1.54)	1.08 (0.91-1.28)

Source: Table 14.2.1.6

Table 2.1-6 Subjects With at Least a 4-fold Increase in hSBA Titers

Serogroup	Study Day	Percentage (95% CI)	
		ACWY Group	Control Group
		N=15	N=14
A	Day 8	7% (0%-32%)	0% (0%-23%)
	Day 29	20% (4%-48%)	0% (0%-23%)
C	Day 8	20% (4%-48%)	0% (0%-23%)
	Day 29	27% (8%-55%)	0% (0%-23%)
W	Day 8	7% (0%-32%)	0% (0%-23%)
	Day 29	13% (2%-40%)	0% (0%-23%)
Y	Day 8	20% (4%-48%)	0% (0%-23%)
	Day 29	27% (8%-55%)	0% (0%-23%)

Source: Table 14.2.1.3

Table 2.1-7 Subjects With at Least a 4-fold Increase in ELISA GMCs

Serogroup	Study Day	Percentage (95% CI)	
		ACWY Group	Control Group
		N=15	N=14
A	Day 8	0% (0%-22%)	0% (0%-23%)
	Day 29	7% (0%-32%)	0% (0%-23%)
C	Day 8	0% (0%-22%)	0% (0%-23%)
	Day 29	7% (0%-32%)	0% (0%-23%)
W	Day 8	0% (0%-22%)	0% (0%-23%)
	Day 29	0% (0%-22%)	0% (0%-23%)
Y	Day 8	0% (0%-22%)	0% (0%-23%)
	Day 29	0% (0%-22%)	0% (0%-23%)

Source: Table 14.2.1.5

Table 2.1-8 Overview of Reactogenicity

	ACWY Group N=15		Control Group N=14	
	Subject N (%)		Subject N (%)	
Local reactions	**All**	**Severe**	**All**	**Severe**
Erythema	0	0	1 (7%)	0
Induration	0	0	0	0
Swelling	1 (7%)	0	0	0
Pain	9 (60%)	0	6 (43%)	0
Systemic reactions	**All**	**Severe**	**All**	**Severe**
Malaise	3 (20%)	0	0	0
Chills	0	0	1 (7%)	0
Headache	3 (20%)	0	4 (29%)	0
Nausea	1 (7%)	0	1 (7%)	0
Myalgia	4 (27%)	0	2 (14%)	0
Arthralgia	0	0	0	0
Other				
Axillary temperature ≥ 38°C	0		0	
Stayed home due to reaction	0		0	
Analgesics/antipyretics	2 (13%)		2 (14%)	

Source: Table 14.3.1.1.3

2.0 SYNOPSIS

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Title of study: A Phase II, Randomized, Observer-Blind, Active Controlled, Multi-center, Dose Ranging Study to Evaluate the Immunogenicity and Safety of Different Formulations of Chiron Conjugate Meningococcal ACWY Vaccine and Chiron Conjugate Meningococcal C Vaccine (Menjugate™) Administered To Healthy Toddlers Aged 12-16 Months

Protocol number: V59P2

Coordinating Investigator and Principal Investigator for Finland:
Prof. Timo Vesikari, MD. University of Tampere Medical School. 33014 Tampere, Finland

Principal Investigator and L.K.P. for Germany:
Prof. Heinz J Schmitt, MD. Johannes Gutenberg-University. 55101 Mainz, Germany

Study centers:
Site 1 (Coordinator): University of Tampere Medical School. 33014 Tampere, Finland

01 Tampere Clinic, Hämeenkatu 18 A FIN-33200 - Tampere
02 Pori Clinic, Maantiekatu 32 FIN-28120 - Pori
03 Turku Clinic, Lemminkäisenkatu 14-18 B FIN-20520 - Turku
04 Espoo Clinic Heikintori, 3rd floor Kauppamiehentie 1 FIN-02100 - Espoo
05 Jyväskylä Clinic, Yliopistonkatu 34 A, 2nd floor FIN-40100 - Jyväskylä
06 Lahti Clinic, Kauppakatu 6 A FIN-15140 - Lahti
07 Vantaa East Clinic, Vernissakatu 6 FIN-01300 - Vantaa
08 Kuopio Clinic, Käsityökatu 18 FIN-70100 - Kuopio
09 Oulu Clinic, Kauppurienkatu 23 FIN-90100 – Oulu

Germany:
Site 2: Practice Dr. U. Behre, Hauptstraße 240, 77694 Kehl
Site 3: Practice Dr. L. Sander, Salinenstraße 35, 55543 Bad Kreuznach
Site 4: Practice Dipl. med. B. Klaaßen, In den Weingärten 37, 55276 Oppenheim

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Site 5: Practice Dr. R. Kappes, Auf'm Plätzle 1, 87435 Kempten
Site 6: Dr. Katalin Karsten, Am Waldeck 4, 66763 Dillingen
Site 7: Drs. Johannes und Katrin Kandzora, Am Teich 11, 24534 Neumünster
Site 8: Dr. Rossius, Rendsburger Str. 29, 25534 Neumünster

Publication (reference): None

Study period: (date of first enrollment): 02 JUN 03 (date of last completed): 04 NOV 03	**Phase of development:** Phase 2

Objectives:

Immunogenicity:
Primary

To evaluate the serum bactericidal antibodies (SBA) geometric mean titer (GMT) increase at 1 month after the first study vaccination as compared to baseline values (day 1) in all subjects.

Secondary

To evaluate the immunogenicity of one and two injections of the different formulations of study vaccines for all serogroups in terms of:

- SBA GMT increase at 1 month after the second study vaccination compared with baseline values (day 1) in subjects receiving two doses;
- percentage of subjects with SBA titer ≥ 1:4 at 1 month after the first vaccination in all subjects;
- percentage of subjects with SBA titer ≥ 1:4 at 1 month after the second vaccination in subjects receiving two doses;

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- percentage of subjects with SBA titer ≥ 1:8 at 1 month after the first vaccination in all subjects;
- percentage of subjects with SBA titer ≥ 1:8 at 1 month after the second vaccination in subjects receiving two doses;
- percentage of subjects with at least a 4-fold increase of SBA titers at 1 month after first vaccination compared with baseline values in all subjects;
- percentage of subjects with at least a 4-fold increase of SBA titers at 1 month after the second vaccination compared with baseline values in subjects receiving two doses;
- ELISA (total IgG) geometric mean concentration (GMC) before (day 1) and at 1 month after the first vaccination in all subjects;
- ELISA (total IgG) GMC before (day 1) and at 1 month after the second vaccination in subjects receiving two doses.

In addition:

- for each serogroup, pairwise evaluations were made between each study group (I to VI) for the proportion of subjects with an SBA ≥ 1:4 and SBA ≥ 1:8 at 1 month after each of the study vaccinations.

Safety objectives

To evaluate the safety and tolerability of one and two doses of different formulations of all study vaccines.

Methodology:

This was a phase II, randomized, multi-national, multi-center, active-controlled, observer-blind, dose-ranging study.

Up to 600 healthy toddlers aged 12 to 16 months were to be enrolled and randomly

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assigned in a 1:1:1:1:1:1 ratio to one of the six treatment groups (group I to VI). Within each vaccination group, subjects were also randomized in a 3:1 ratio to receive 1 OR 2 intramuscular (IM) doses of either Novartis Men ACWY conjugate vaccine containing different formulations of meningococcal antigens (10 µg, 5 µg, and 2.5 µg) OR Men CWY alone (group II), OR Novartis Menjugate as control (group VI).

Group (Label)[a]	**Men A (µg)**	**Men C (µg)**	**Men W (µg)**	**Men Y (µg)**	**Subjects receiving 1st dose**	**Subjects receiving 2nd dose**
I (ACWY10)	10	10	10	10	100	25
II (CWY10)	-	10	10	10	100	25
III (A10CWY5)	10	5	5	5	100	25
IV (ACWY5)	5	5	5	5	100	25
V (ACWY2.5)	2.5	2.5	2.5	2.5	100	25
VI (C10)	-	10 (Menjugate)	-	-	100	25

a When needed, the number of injections has been appended to the label, e.g., A10CWY5x2, CWY10x1.

Blood was drawn on visit 1 (day 1, prior to vaccination) and on visit 2 (28 to 35 days after visit 1) in all subjects.

Another blood sample was drawn on visit 3 (28 to 35 days after visit 2) in the subset of subjects receiving two doses.

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Subjects were included in the study if in good health as judged by physical examination and medical history and if they met all inclusion criteria and no exclusion criteria.

Vaccines were administered IM in the thigh region. Subjects remained in the clinic for 30 minutes after vaccination in case of any immediate hypersensitivity reactions.

Parents/legal guardians were then instructed to complete a diary card to describe local reactions (tenderness, erythema, induration, swelling), systemic reactions (change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea), analgesic or antipyretic use, and to record rectal temperature measurements, daily for 7 days following vaccination.

All adverse events were collected for 7 days following vaccination.

All serious adverse events and adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

If an adverse event remained unresolved at the conclusion of the study, a clinical assessment was made by the investigator and the Sponsor physician to determine whether continued follow-up of the adverse event was warranted.

A telephone call was made to check the subjects' health status on the 3rd (+1) and 7th (+1) day after each vaccination. On visit 2 (and on visit 3 in the subset of subjects receiving two doses), diary cards were collected.

All subjects receiving at least one vaccination were included in the safety analyses.

All subjects providing baseline blood samples and at least one postvaccination sample within the protocol-specified time interval were included in the immunogenicity analyses.

Number of subjects (planned and analyzed):

It was expected that, allowing for a 10% drop out rate, by enrolling 600 subjects approximately 540 would be evaluable at visit 2. The subjects were randomly assigned, in a 1:1:1:1:1:1 ratio, into one of the six vaccination groups. The table below shows the number of subjects, planned and actual, enrolled into each group.

Group	Subjects enrolled		Subjects receiving first vaccination		Subjects receiving second vaccination	
	Planned	Actual	Planned	Actual	Planned	Actual
I	100	112	100	109	25	27
II	100	109	100	106	25	28
III	100	107	100	103	25	24
IV	100	101	100	101	25	27
V	100	105	100	104	25	25
VI	100	101	100	97	25	24

In groups I, II, III, IV, V, and VI, the safety analysis comprised 109, 106, 102, 101, 104, and 97 subjects, and the per-protocol (PP) immunogenicity analysis comprised 105, 97, 97, 100, 100, and 92 subjects, respectively.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria
Individuals eligible for enrollment into this study were male and female healthy toddlers who were:

1. 12 to 16 months of age, whose parents or legal guardian had given written informed consent prior to study entry
2. available for all the visits scheduled in the study
3. in good health as determined by:
   - medical history
   - physical examination
   - clinical judgment of the investigator

Exclusion Criteria
Individuals were not enrolled into the study if:

1. their parents or legal guardians were unwilling or unable to give written informed consent to participate in the study
2. they had had laboratory confirmed *N meningitidis* infection or a history of a previous disease potentially related to any Meningococcal infection
3. they had had household contact and/or intimate exposure in the 30 days prior to planned enrollment to an individual with ascertained *N meningitidis* serogroup A or C or W or Y disease

4. they had experienced within the previous 7 days significant acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy or they had experienced fever ≥ 38°C within the 3 days prior to planned enrollment
5. they had any serious chronic disease such as cardiac, autoimmune disease or insulin dependent diabetes
6. they had a known or suspected impairment/alteration of immune function resulting from:
   - receipt of immunosuppressive therapy (any cortical steroid or cancer chemotherapy)
   - receipt of immunostimulants
   - receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 90 days prior to planned enrollment and for the full length of the study
   - suspected or known HIV infection or HIV related disease
7. they had received another vaccine within the 30 days prior to planned enrollment
8. they had received any investigational agent within the 90 days prior to planned enrollment
9. they had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component
10. they had been immunized with any meningococcal polysaccharide or conjugate vaccine
11. they had any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives
12. their families were planning to leave the area of the study site before the end of the study period.

Test product, dose, mode of administration, lot number:
Groups I, III, IV, V received different formulations of the investigational Novartis Men ACWY vaccine obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be resuspended with the Men CWY full liquid vaccine.

Vial	Vaccine	Lot No.	Expiry Date
A	MenA 10µg	005011	12/2003
B	MenC, W, Y 10µg	T79P19D1	12/2003
C	MenC, W, Y 5µg	T79P20D1	12/2003
D	MenA 5µg	006011	12/2003
E	MenC, W, Y 2.5µg	T79P21D1	12/2003

One or two doses of the Novartis Men ACWY vaccine were injected IM in the thigh region.

After reconstitution, Novartis Men ACWY vaccine had the following composition per 0.5 mL of injectable suspension:

Vaccine Group	**I**	**III**	**IV**	**V**
MenA-CRM_{197} conjugate	10 µg	10 µg	5 µg	2.5 µg
MenC-CRM_{197} conjugate	10 µg	5 µg	5 µg	2.5 µg
MenW-CRM_{197} conjugate	10 µg	5 µg	5 µg	2.5 µg
MenY-CRM_{197} conjugate	10 µg	5 µg	5 µg	2.5 µg
Aluminum phosphate	0.3 mg Al^{3+}			
Sodium chloride	(b) (4)			
(b) (4)	(b) (4)			(b) (4)
Sodium phosphate buffer	(b) (4)			
Potassium dihydrogen phosphate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)			
WFI	q.s to 0.5 mL			

Group II received the investigational Novartis Men CWY full liquid vaccine alone which had the following composition per 0.5 mL of injectable suspension:

MenC-CRM_{197} conjugate	10 µg
MenW-CRM_{197} conjugate	10 µg
MenY-CRM_{197} conjugate	10 µg
Aluminum phosphate	0.3 mg Al^{3+}
Sodium chloride	(b) (4)
Sodium phosphate buffer	(b) (4)
(b) (4)	(b) (4)
WFI	q.s to 0.5 mL

One or two doses of the Novartis Men CWY vaccine were injected IM in the thigh region.

Duration of study:
Enrollment period: 12 weeks.
Maximum participation per subject: 8 weeks

Reference therapy, dose, mode of administration, lot number:
Group VI received licensed Novartis Menjugate obtained by extemporaneous mixing just before injection of the lyophilized Men C component to be resuspended with the solvent (aluminum hydroxide) supplied.

Vial F: (Menjugate) MenC 10µg
Lot No. SA5279A Expiry date: 12/2003

Vial G: Solvent
Lot No. 3201 Expiry date: 05/2004

After reconstitution Novartis Menjugate had the following composition per 0.5 mL of injectable suspension:

MenC-CRM$_{197}$ conjugate	10 µg
Aluminum hydroxide	0.3 to 0.4 mg Al^{3+}
Sodium chloride	3.5 mg
Mannitol	7.3 mg
Sodium phosphate monobasic	0.92 mg
Sodium phosphate dibasic	0.48 mg
WFI	q.s to 0.5 mL

One or two 0.5 mL doses of Novartis Menjugate were injected IM in the thigh region.

Criteria for evaluation:

Immunogenicity

The immunogenicity of one or two injections of the different formulations of the study vaccines were evaluated for each serogroup in terms of:

- SBA GMT increase at 1 month after the first vaccination as compared to baseline values (day 1) in all subjects
- SBA GMT increase at 1 month after the second vaccination as compared to baseline values (day 1) in subjects receiving two doses
- percentage of subjects with SBA titer ≥ 1:4 at 1 month after the first vaccination in all subjects
- percentage of subjects with SBA titer ≥ 1:4 at 1 month after the second vaccination in subjects receiving two doses
- percentage of subjects with SBA titer ≥ 1:8 at 1 month after the first vaccination in all subjects
- percentage of subjects with SBA titer ≥ 1:8 at 1 month after the second vaccination in subjects receiving two doses
- percentage of subjects with a 4-fold increase of SBA titers at 1 month after the first vaccination compared to baseline values in all subjects
- percentage of subjects with a 4-fold increase of SBA titers at 1 month after the second vaccination compared to baseline values in subjects receiving two doses
- ELISA (total IgG) GMCs before (day 1) and 1 month after the first vaccination in all subjects
- ELISA (total IgG) GMCs before (day 1) and 1 month after the second vaccination in subjects receiving two doses

Safety

Criteria for assessing safety objective included observed local reactions at the site of injection (i.e., tenderness, erythema, induration, swelling) and systemic reactions (i.e., change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea), rectal temperature, analgesic or antipyretic use for 7 days postvaccination. All adverse

events during the 7 days after each vaccination were collected; serious adverse events and/or adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

Statistical methods:
Statistical hypothesis: There was no statistical (null) hypothesis associated with the immunogenicity objective. All analyses were run descriptively, with the aim to suggest hypotheses to be tested in future, properly powered studies.

Summary and Conclusions:
A total of 635 subjects were enrolled in the study and randomized to one of the six study vaccine groups. Nine study sites in Finland enrolled 540 subjects, and seven study sites in Germany enrolled 95 subjects. Six hundred twenty (620) of the 635 randomized subjects were exposed to study vaccines, and 15 subjects were withdrawn before administration of study vaccine due either to inappropriate enrollment when late-arriving screening results indicated that the subjects did not meet study eligibility criteria or to withdrawal of consent. Six hundred seven (607) of the 635 randomized subjects completed the study, and 28 subjects were withdrawn prematurely, including 13 subjects who withdrew consent, 8 subjects who were inappropriately enrolled, 3 subjects who were withdrawn due to an AE, 2 subjects each who were withdrawn due to loss to follow-up or due to protocol deviation. One hundred fifty-five (155) of the 620 vaccinated subjects received a second injection of study vaccines.

Subjects were 12 to 17 months of age, and mean ages by vaccine group ranged from 14.1 to 14.4 months. The distribution of sexes was similar among the vaccine groups (range of male subjects per group was 49% to 55%). Nearly all subjects were Caucasian (97% to 98% per group). Mean body weights of subjects ranged from 10.50 to 10.65 kg among the groups, and mean height ranged from 78.81 to 79.27 cm. No notable differences in demographic characteristics among the vaccine groups were apparent for the modified ITT sample, the per-protocol sample, or the safety sample.

Immunogenicity results

Primary Immunogenicity Analysis:

Increase in SBA Using Human Complement (hSBA) Titers After First Vaccination
By 28 to 35 days after the first vaccination, hSBA titers in all four Men ACWY vaccine groups were highest to serogroup Y, were intermediate to serogroups C and W, and were lowest to serogroup A (refer to **Synopsis Table 2-2**).

Each study vaccine group containing the A antigen was immunogenic (geometric mean ratio [GMR] range = 1.89 to 2.83) against serogroup A, and the A10CWY5 vaccine group was clearly more immunogenic (GMR = 2.83) than the other A-antigen-containing groups (ACWY10 = 1.94, ACWY5 = 1.92, and ACWY2.5 = 1.89), as the 95% confidence intervals (CIs) for the A10CWY5 group did not overlap those of the other groups. The CWY10 and the C10 (Menjugate) control groups did not contain the A antigen, did not raise the titers against the A serogroup, and were not immunogenic.

Each study vaccine group containing the C antigen was immunogenic (GMR range = 2.24 to 4.29) against serogroup C. The C10 (Menjugate) control was more immunogenic (GMR = 4.29) than the ACWY2.5group (GMR = 2.55) and the ACWY5

group (GMR = 2.24), marginally more immunogenic (small CI overlap) than the A10CWY5 group (GMR = 2.6), and similar in immunogenicity to the ACWY10 and CWY10 groups (GMRs = 3.1 and 3.34, respectively).

Each study vaccine group containing the W antigen was immunogenic (GMR range = 3.24 to 4.04) against serogroup W, and there were no apparent differences among the five study vaccines. Similarly, each study vaccine group containing the Y antigen was immunogenic (GMR range = 4 to 6.1) against serogroup Y, and there were no apparent differences among the five study vaccines. The C10 (Menjugate) control did not contain the W or Y antigens, did not raise the titers, and was not immunogenic against the W or Y serogroups.

After the first vaccination, there was no evidence of interference or reduction in immunogenicity of the ACWY10 vaccine against any of the four serogroups by reason of the presence of the A antigen, based on GMR comparisons with CWY10 vaccine group.

The **ACWY10** and **A10CWY5** vaccines were more immunogenic 28 to 35 days after the first vaccination at German sites than at Finnish sites against all four serogroups. The **C10 (Menjugate) control** was also more immunogenic after the first vaccination against the C serogroup at German than at Finnish sites.

Secondary Immunogenicity Analyses:

Increase in hSBA Titers After Second Vaccination

In each instance in which the vaccine formulation contained the serogroup antigen, the second vaccination boosted hSBA titers at 28 to 35 days following the second vaccination by 5- to 20-fold above that observed after the first vaccination (**Synopsis Table 2-3**). After the second vaccination, antibody response in all four Men ACWY vaccine groups to serogroup C was highest, to serogroup Y was intermediate, and to serogroups W and A was lowest.

By 28 to 35 days after the second vaccination, each study vaccine group containing the A, W, and Y antigens was immunogenic (GMR range: serogroup A = 6.91 to 14; serogroup W = 10 to 14; serogroup Y = 17 to 34) against the respective serogroup, and no notable differences in immunogenicity were apparent between these groups. Each study vaccine group containing the C antigen was immunogenic (GMR range = 24 to 79) against serogroup C. The C10 (Menjugate) control was more immunogenic (GMR = 79) than the ACWY5 group (GMR = 24), marginally more immunogenic than the ACWY2.5 group (GMR = 35), and similar in immunogenicity to the ACWY10, CWY10, and A10CWY5 groups (GMRs = 44, 50, and 38, respectively).

There was no evidence after the second vaccination of interference or reduction in immunogenicity of the ACWY10 vaccine against any of the four serogroups by reason of the presence of the A antigen, based on GMR comparisons with CWY10 vaccine group. No consistent differences in immunogenicity were apparent between German and Finnish sites.

Percentages of Subjects with hSBA Titers 1:4 or Greater

Similar to primary immunogenicity results, the percentages of subjects with hSBA titers

of 1:4 or greater increased from before to one month after the first vaccination and were highest against serogroup Y, were intermediate against serogroups C and W, and were lowest to serogroup A in all four Men ACWY vaccine groups **(Synopsis Table 2-4)**.

Each study vaccine group containing the A antigen was immunogenic (range = 32% to 55%) against serogroup A after the first vaccination. The A10CWY5 vaccine group was clearly more immunogenic (55%) than the ACWY10 group (32%) and marginally more immunogenic than the ACWY5 and ACWY2.5 groups (37% and 39%, respectively).

Each vaccine group containing the C antigen was immunogenic (range = 42% to 77%) against serogroup C after the first vaccination. The C10 (Menjugate) control was more immunogenic against the C serogroup than all vaccine groups except the CWY10 group. The C10 (Menjugate) control was clearly more immunogenic (77%) than the ACWY10, A10CWY5, ACWY5, and ACWY2.5 groups (56%, 49%, 42%, and 50%, respectively) and marginally more immunogenic than the CWY10 group (GMT = 59%).

Each group containing the W and Y antigens was immunogenic (range: serogroup W = 53% to 58%; serogroup Y = 56% to 70%) against the respective serogroups after the first vaccination, and there were no apparent differences among the five study vaccines.

By 28 to 35 days after the second vaccination, in each instance in which the vaccine formulation contained the serogroup antigen, the second vaccination boosted the percentages of subjects with hSBA titers of 1:4 or greater by approximately 1.5- to 2-fold above those observed after the first vaccination. Percentages of subjects with hSBA titers of 1:4 or greater increased to 80% to 100% against serogroup A; to 96% to 100% against serogroup C, to 79% to 96% against serogroup W, and to 92% to 96% against serogroup Y.

Percentages of Subjects with hSBA Titers 1:8 or Greater

Results obtained using a more conservative threshold for immunogenicity of hSBA titers of 1:8 or greater were similar to, and confirmed, those described for the 1:4 or greater threshold (**Synopsis Table 2-5**).

Percentages of Subjects with 4-Fold Increases in hSBA Titers

Results obtained using another common threshold for immunogenicity, the percentages of subjects with 4-fold or greater increases in hSBA titers, were similar to those described previously **(Synopsis Table 2-6)**.

Safety results

Reactogenicity

Fifty-six percent (56%) to 73% of the subjects in groups that received a single vaccination and 46% to 64% of the subjects in groups that received two vaccinations experienced at least one reactogenicity event. Overall reactogenicity rates were similar in Finland and Germany. After the first vaccination, tenderness (range 28% to 41% of subjects across all six vaccine groups) and erythema (range 4% to 11%) were the most commonly experienced local reactions. Erythema, induration, and swelling (range 1% to 11%) were infrequently reported.

The most commonly experienced systemic reactions were irritability (range 32% to 38%), sleepiness (range 18% to 30%), and change in eating habits (range 8% to 19%). Four subjects reported erythema greater than 50 mm in size, and one subject experienced severe tenderness (cried when limb moved). The percentages of subjects experiencing local reactions, systemic reactions, and other indicators of reactogenicity were low and similar among the six vaccine groups.

Treatment-Emergent Adverse Events

During the period after first vaccination and before second vaccination (or study termination for subjects receiving one dose), 30% to 50% of each group experienced at least one treatment-emergent adverse event (AE) (among all 620 subjects, regardless of relationship of the event to study vaccine). AEs experienced by the largest percentages of subjects after the first vaccination, regardless of treatment relationship, were otitis media (26 of 620 vaccinated subjects = 4.2%), diarrhea (3.7%), pyrexia (3.7%), respiratory tract infection (3.4%), rhinitis (2.6%), upper respiratory tract infection (2.3%), cough (1.9%), conjunctivitis (1.8%), arthropod bite (1.8%), and teething (1.6%).

All AEs but two observed following the first vaccination were mild or moderate in intensity. The two severe AEs were wheezing experienced by a subject in the ACWY10x2 group and convulsion, a serious adverse event (SAE), experienced by a subject in the ACWY2.5x1 group. Neither of these severe AEs was considered related to study vaccines by the investigator.

Probably or possibly vaccine-related AEs experienced by the largest percentages of subjects after the first vaccination were rhinorrhea (7 of 620 subjects = 1.1%), diarrhea, irritability, pyrexia, injection site erythema, nasopharyngitis, respiratory tract infection, eating disorder, restlessness, and erythema (less than 1% each).

During the period from the second vaccination to study termination, 25% to 50% of subjects who received a second vaccination according to the randomization code (two-dose subset) experienced at least one treatment-emergent AE. AEs experienced by the largest percentages of subjects, regardless of treatment relationship, were otitis media (12 of 155 vaccinated subjects = 7.7%), pyrexia (4.5%), conjunctivitis (3.9%), diarrhea (3.2%), upper respiratory tract infection (3.2%), rhinitis (2.6%), viral infection (2.6%), teething (1.9%), respiratory tract infection (1.9%), rhinorrhea (1.9%), and erythema (1.9%).

All AEs but one observed following the second vaccination were mild or moderate in intensity. The severe AE was irritability experienced by a subject in the CWY10x2 group. This AE was considered to be possibly related to study vaccine by the investigator.

Probably or possibly vaccine-related AEs experienced by the largest percentages of subjects after the second vaccination were diarrhea and erythema (3 of 155 subjects = 2% each), irritability (1%), and single instances of injection site erythema, injection site induration, pyrexia, otitis media, tonsillitis, upper respiratory tract infection, somnolence, crying, eating disorder, insomnia, restlessness, rhinorrhea, and atopic dermatitis (less than 1% each).

No deaths were reported during the study.

Two SAEs were reported during the study, both of which were considered to be not related to study vaccine: one subject in the A10CWY5x2 group experienced moderate gastroenteritis, and one subject in the ACWY2.5x1 group experienced a single, continuous instance of severe convulsion. Both subjects continued participation in the study.

Three subjects experienced AEs that led to premature withdrawal from the study before the second vaccination, including moderate varicella, mild upper abdominal pain, and mild respiratory infection. These AEs were considered to be not related to study vaccines by the investigator.

One subject experienced a delay in receiving the second vaccination due to balanitis. The subject was treated with prescription antibiotics and was withdrawn from the study due to protocol violation. This AE was considered to be not related to study vaccine by the investigator.

Conclusions

The immunogenicity results after the first study vaccination showed that the A10CWY5 formulation produced the highest hSBA titers against serogroups A and Y among the Novartis Men ACWY formulations during the study (**Synopsis Table 2-7**). These results were consistent regardless of the method of measurement used as an indicator of immunogenicity. The C10 (Menjugate) control produced higher hSBA titers against serogroup C than any of the Men ACWY formulations, and the CWY10 formulation without the A antigen produced the highest responses to serogroup W.

Approximately 25% of study subjects received a second study vaccination. Results showed that the second vaccination boosted the protection afforded by a single vaccination, and high hSBA titers and high percentages of subjects achieving 1:4 and 1:8 thresholds against all four serogroups were consistently produced.

All Novartis MenACWY formulations were well tolerated and immunogenic in toddlers aged 12 to 17 months.

The results of the study led to the selection of the optimal antigen ratios, i.e., 10 µg Men A and 5 µg of Men C, MenW-135, and Men Y, to be used for further development.

Table 2-1 Time and Events

	All subjects				Only subjects receiving 2 doses		
Study Visit Day	**1**	**Phone Call☎**	**Phone Call☎**	**29 (+7)**	**Phone Call☎**	**Phone Call☎**	**57 (+7)**
Visit N°	**1**			**2**			**3**
Study Day Number	**1**	**2 (+1)**	**7 (+1)**	**28-35 days after visit 1**	**2 days (+1) after visit 2**	**7 days (+1) after visit 2**	**28-35 days after visit 2**
Obtain Informed Consent	X						
Medical History	X						
Complete Physical Examination	X			X			X
Screen for Inclusion/Exclusion Criteria	X						
Follow-up Telephone Call		X	X		X	X	
Blood Draw for Assays	X			X			X
Measure Rectal Temperature	X			Xa			
Immunization	X			Xb			
Injection-site Examination	X			X			X
Assess Local/Systemic Reactions	X	X	X	X	X	X	X
Assess Concomitant Medications	X	X	X	X	X	X	X
Assess Adverse Events	X	X	X	X	X	X	X
Diary Card Review				Xd			Xd
Complete Study Termination				Xc			X

Xa = before the second dose of the vaccine was administered to subjects belonging to the "2-dose" regimen
Xb = second dose administered only to subjects belonging to the "2-dose" regimen
Xc = if subject belonged to the "2-dose" regimen the study termination was completed in visit 3
Xd = collect diary card and reconcile with the data recorded during phone interviews on the Local and Systemic Reaction case report form (CRF) page

Table 2-2 Primary Immunogenicity Analysis Summary: Increase in hSBA Geometric Mean Titers at One Month After the First Vaccination

Serogroup	Randomized Vaccine Group Geometric Mean Ratio (GMR) of hSBA Geometric Mean Titer (GMT) at One Month After First Vaccination : GMT at Baseline (Day 1)					
	I ACWY10 n = 112	**II CWY10 n = 109**	**III A10CWY5 n = 107**	**IV ACWY5 n = 101**	**V ACWY2.5 n = 105**	**VI C10 n = 101**
Men A GMR (95% CIs) n	1.94 (1.64-2.31) 102	1 (0.82-1.22) 75	2.83 (2.37-3.38) 96	1.92 (1.61-2.28) 100	1.89 (1.59-2.25) 100	1 (0.81-1.24) 67
Men C GMR (95% CIs) n	3.1 (2.47-3.89) 103	3.34 (2.58-4.32) 79	2.6 (2.05-3.29) 95	2.24 (1.78-2.82) 100	2.55 (2.03-3.21) 100	4.29 (3.26-5.65) 70
Men W GMR (95% CIs) n	3.29 (2.55-4.24) 102	4.04 (3.03-5.39) 79	3.41 (2.62-4.42) 96	3.24 (2.51-4.19) 100	3.36 (2.6-4.34) 100	1 (0.73-1.36) 69
Men Y GMR (95% CIs) n	4 (3.01-5.31) 101	4.67 (3.34-6.55) 72	6.1 (4.54-8.2) 94	4.73 (3.54-6.32) 98	5.92 (4.45-7.89) 100	1.05 (0.72-1.52) 60

Sources: Tables 11.4.1.1-2 and 14.2.1.1.

Table 2-3 Increase in hSBA Geometric Mean Titers at One Month After the Second Vaccination

Serogroup	Randomized Vaccine Group Geometric Mean Ratio (GMR) of hSBA Geometric Mean Titer (GMT) at One Month After Second Vaccination : GMT at Baseline (Day 1)					
	I ACWY10 n = 29	**II CWY10 n = 30**	**III A10CWY5 n = 28**	**IV ACWY5 n = 29**	**V ACWY2.5 n = 25**	**VI C10 n = 27**
Men A GMR (95% CIs) n	14 (8.8-21) 25	1 (0.56-1.78) 14	14 (9.18-23) 23	6.91 (4.5-11) 25	8.4 (5.46-13) 25	1 (0.64-1.57) 23
Men C GMR (95% CIs) n	44 (28-69) 26	50 (28-90) 15	38 (24-61) 23	24 (15-37) 26	35 (22-56) 25	79 (49-128) 22
Men W GMR (95% CIs) n	11 (6.71-17) 27	12 (6.21-23) 14	14 (8.37-24) 22	10 (6.29-16) 26	12 (7.13-19) 25	1 (0.59-1.68) 22
Men Y GMR (95% CIs) n	19 (12-30) 27	34 (18-63) 15	29 (17-48) 22	17 (11-28) 26	26 (16-43) 25	1 (0.6-1.68) 22

Sources: Tables 11.4.1.2.1-1 and 14.2.1.2.

Table 2-4 Percentage of Subjects With hSBA Titers of 1:4 or Greater at One Month After the First and Second Vaccinations

Serogroup	Randomized Vaccine Group Percentage of Subjects with hSBA Titers of ≥ 1:4 at One Month After the First and Second Vaccinations					
	I ACWY10 n = 112	**II CWY10 n = 109**	**III A10CWY5 n = 107**	**IV ACWY5 n = 101**	**V ACWY2.5 n = 105**	**VI C10 n = 101**
One Month After First Vaccination						
Men A % (95% CIs) n	32 (23-42) 102	0 (0-5) 75	55 (45-65) 96	37 (28-47) 100	39 (29-49) 100	0 (0-5) 67
Men C % (95% CIs) n	56 (46-66) 103	59 (48-70) 79	49 (39-60) 95	42 (32-52) 100	50 (40-60) 100	77 (66-86) 70
Men W % (95% CIs) n	56 (46-66) 102	58 (47-69) 79	53 (43-63) 96	54 (44-64) 100	56 (46-66) 100	0 (0-5) 69
Men Y % (95% CIs) n	56 (46-66) 101	61 (49-72) 72	70 (60-79) 94	64 (54-74) 98	66 (56-75) 100	2 (0.042-9) 60
One Month After Second Vaccination						
Serogroup	**I ACWY10 n = 29**	**II CWY10 n = 30**	**III A10CWY5 n = 28**	**IV ACWY5 n = 29**	**V ACWY2.5 n = 25**	**VI C10 n = 27**
Men A % (95% CIs) n	100 (86-100) 25	0 (0-23) 14	91 (72-99) 23	84 (64-95) 25	80 (59-93) 25	0 (0-15) 23
Men C % (95% CIs) n	100 (87-100) 26	100 (78-100) 15	96 (78-100) 23	96 (80-100) 26	100 (86-100) 25	100 (85-100) 22
Men W % (95% CIs) n	96 (81-100) 27	79 (49-95) 14	95 (77-100) 22	88 (70-98) 26	80 (59-93) 25	0 (0-15) 22
Men Y % (95% CIs) n	96 (81-100) 27	93 (68-100) 15	95 (77-100) 22	96 (80-100) 26	92 (74-99) 25	0 (0-15) 22

Sources: Tables 11.4.1.2.2-1 and 14.2.1.3.

Table 2-5 Percentage of Subjects With hSBA Titers of 1:8 or Greater at One Month After the First and Second Vaccinations

Serogroup	Randomized Vaccine Group Percentage of Subjects with hSBA Titers of ≥ 1:8 at One Month After the First and Second Vaccinations					
	I ACWY10 n = 112	**II CWY10 n = 109**	**III A10CWY5 n = 107**	**IV ACWY5 n = 101**	**V ACWY2.5 n = 105**	**VI C10 n = 101**
One Month After First Vaccination						
Men A % (95% CIs) n	25 (17-34) 102	0 (0-5) 75	39 (29-49) 96	23 (15-32) 100	25 (17-35) 100	0 (0-5) 67
Men C % (95% CIs) n	44 (34-54) 103	44 (33-56) 79	34 (24-44) 95	30 (21-40) 100	34 (25-44) 100	49 (36-61) 70
Men W % (95% CIs) n	45 (35-55) 102	49 (38-61) 79	45 (35-55) 96	44 (34-54) 100	39 (29-49) 100	0 (0-5) 69
Men Y % (95% CIs) n	47 (37-57) 101	51 (39-63) 72	64 (53-73) 94	51 (41-61) 98	59 (49-69) 100	2 (0.042-9) 60
One Month After Second Vaccination						
Serogroup	**I ACWY10 n = 29**	**II CWY10 n = 30**	**III A10CWY5 n = 28**	**IV ACWY5 n = 29**	**V ACWY2.5 n = 25**	**VI C10 n = 27**
Men A % (95% CIs) n	92 (74-99) 25	0 (0-23) 14	87 (66-97) 23	60 (39-79) 25	72 (51-88) 25	0 (0-15) 23
Men C % (95% CIs) n	100 (87-100) 26	100 (78-100) 15	96 (78-100) 23	92 (75-99) 26	92 (74-99) 25	100 (85-100) 22
Men W % (95% CIs) n	85 (66-96) 27	71 (42-92) 14	95 (77-100) 22	77 (56-91) 26	72 (51-88) 25	0 (0-15) 22
Men Y % (95% CIs) n	93 (76-99) 27	93 (68-100) 15	82 (60-95) 22	92 (75-99) 26	88 (69-97) 25	0 (0-15) 22

Sources: Tables 11.4.1.2.3-1 and 14.2.1.4.

Table 2-6 Percentage of Subjects With 4-Fold or Greater Increases in hSBA Titers at One Month After the First and Second Vaccinations

Serogroup	Randomized Vaccine Group Percentage of Subjects with 4-Fold or Greater Increases in hSBA Titers at One Month After the First and Second Vaccinations					
	I ACWY10 n = 112	**II CWY10 n = 109**	**III A10CWY5 n = 107**	**IV ACWY5 n = 101**	**V ACWY2.5 n = 105**	**VI C10 n = 101**
One Month After First Vaccination						
Men A % (95% CIs) n	25 (17-34) 102	0 (0-5) 75	39 (29-49) 96	23 (15-32) 100	25 (17-35) 100	0 (0-5) 67
Men C % (95% CIs) n	44 (34-54) 103	44 (33-56) 79	34 (24-44) 95	29 (20-39) 100	34 (25-44) 100	49 (36-61) 70
Men W % (95% CIs) n	44 (34-54) 102	49 (38-61) 79	44 (34-54) 96	41 (31-51) 100	39 (29-49) 100	0 (0-5) 69
Men Y % (95% CIs) n	47 (37-57) 101	51 (39-63) 72	64 (53-73) 94	50 (40-60) 98	59 (49-69) 100	2 (0.042-9) 60
One Month After Second Vaccination						
Serogroup	**I ACWY10 n = 29**	**II CWY10 n = 30**	**III A10CWY5 n = 28**	**IV ACWY5 n = 29**	**V ACWY2.5 n = 25**	**VI C10 n = 27**
Men A % (95% CIs) n	92 (74-99) 25	0 (0-23) 14	87 (66-97) 23	60 (39-79) 25	72 (51-88) 25	0 (0-15) 23
Men C % (95% CIs) n	100 (87-100) 26	100 (78-100) 15	96 (78-100) 23	92 (75-99) 26	92 (74-99) 25	100 (85-100) 22
Men W % (95% CIs) n	85 (66-96) 27	71 (42-92) 14	95 (77-100) 22	77 (56-91) 26	72 (51-88) 25	0 (0-15) 22
Men Y % (95% CIs) n	93 (76-99) 27	87 (60-98) 15	82 (60-95) 22	92 (75-99) 26	88 (69-97) 25	0 (0-15) 22

Sources: Tables 11.4.1.2.4-1 and 14.2.1.5.

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Title of study: A Phase II, Open-label, Controlled, Single-Center Study to Evaluate the Immune Response Following One Dose of a Licensed Meningococcal ACWY Polysaccharide Vaccine 6 Months After One Dose of Chiron Meningococcal ACWY Conjugate Vaccine (As Part of V59P2 Study)

Protocol number: V59P2E1

Investigators: Prof. Timo Vesikari, MD

Study centers: University of Tampere Medical School, 33014 Tampere, Finland

Publication (reference): none

Study period: **(date of first enrollment)** 02 FEB 2004 **(date of last completed)** 19 MAY 2004	**Phase of development:** Phase 2

Objectives:

Immunogenicity Objectives

- To evaluate the persistence of antibodies to *N meningitidis* serogroups A, C, W, and Y at least 6 months after vaccination with one dose of Novartis (formerly Chiron) meningococcal ACWY conjugate vaccine (MenACWY).
- To evaluate the anamnestic response to *N meningitidis* serogroups A, C, W, and Y after challenge with one dose of a licensed meningococcal ACWY polysaccharide vaccine (PS ACWY) at least 6 months after vaccination with one dose of Novartis MenACWY, as compared to the immunological response of 24-month-old naïve subjects receiving one dose of a licensed PS ACWY.

Safety Objective

- To monitor the safety of all study subjects during the study period.

Methodology:

This was a phase 2, open-label, controlled, single-center study.

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Healthy children having previously participated in Novartis study V59P2 in Finland and aged 22 to 24 months inclusive were enrolled into this study to evaluate the persistence of antibodies at least 6 months after vaccination with one dose of different formulations of Novartis meningococcal ACWY conjugate vaccine (MenACWY), all containing aluminum phosphate (groups I to V of study V59P2; see table in the Synopsis section "Number of subjects [planned and analyzed]").

These children were also to receive one full dose of a licensed meningococcal ACWY polysaccharide vaccine (PS ACWY) to assess induction of immunological memory.

In addition, a control group of naïve children aged 24 months received one full dose of PS ACWY (group VII of the current study).

Subjects were examined to ensure they were in good health and meet all inclusion criteria and no exclusion criteria. Medical history was obtained and a physical examination performed.

At visit 1 (180 to 240 days after visit 1 of V59P2 study and day 1 for the naïve 24-month-old children), a blood sample was taken to assess antibody persistence in subjects previously primed with MenACWY and to evaluate baseline antibody titers in the naïve group. During the same visit, a full dose of PS ACWY (i.e., 50 µg of each of the four polysaccharide antigens) was administered subcutaneously (SC) in the deltoid region.

At visit 2 (28 to 35 days after visit 1 of the current study), a blood sample was obtained from all subjects vaccinated during visit 1.

All subjects remained in the clinic for 30 minutes after vaccine administration to be monitored for any hypersensitivity reactions and other adverse events (AEs). Subjects' parents/legal representatives were then instructed to complete a diary card to describe local reactions (tenderness, erythema, induration), systemic reactions (change in eating habits, sleepiness, irritability, vomiting, diarrhea, persistent crying lasting more than 3 hours), analgesic or antipyretic medication use, and to record rectal temperature measurements daily for 7 days following vaccination. A telephone call was to be made to check for the subject's status on the third and eighth day after vaccination. Diary cards were to be collected at visit 2.

All adverse events were to be collected for 7 days following vaccination.

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

All serious adverse events (SAEs) and AEs necessitating a physician's visit and/or resulting in premature subject's withdrawal from study were to be collected throughout the study.

If an AE remained unresolved at the conclusion of the study, a clinical assessment was to be made by the investigator and the Novartis physician to determine whether continued follow-up of the AE was warranted.

Number of subjects (planned and analyzed):

Approximately 125 children from V59P2 study aged 22-24 months inclusive having previously received one dose of the Novartis investigational MenACWY were planned to participate in this study (group I-V). In addition, approximately 25 naïve children aged 24 months (group VII) were to receive one full dose of the PS ACWY according to the following scheme:

Original Study V59P2	**Extension Study V59P2E1**		
	PS Vaccine Group	**Visit 1***	**Visit 2****
Single-dose Conj. Group MenACWY (µg)	**ACWY PS Group[a] 50-50-50-50 µg**	**PS then Blood Draw**	**Blood Draw**
		N	
I -- ACWY10x1 10-10-10-10	I -- ACWY10x1	25	
II -- CWY10x1 0-10-10-10	II-- CWY10x1	25	
III -- A10CWY5x1 10-5-5-5	III -- A10CWY5x1	25	
IV -- ACWY5x1 5-5-5-5	IV -- ACWY5x1	25	
V -- ACWY2.5x1 2.5-2.5-2.5-2.5	V -- ACWY2.5x1	25	
VI -- C10x1 0-10-0-0 (Menjugate)	-- V59P2 group VI not studied in this extension study.		
-- V59P2E1 group VII not studied in original V59P2 study	VII - Naïve[b] subjects group	25	
	Total	150	

* 180-240 days after V59P2 study visit 1, ** 28-35 days after visit 1 of study V59P2E1.

[a] all subjects received only PS ACWY vaccination during extension study V59P2E1; V59P2E1 group designations are retained from V59P2 to identify MenACWY regimens received during original study V59P2.

[b] naïve subjects – newly enrolled in extension study V59P2E1; subjects were not enrolled in original study V59P2 and did not receive prior MenACWY.

A total of 119 subjects were actually enrolled; 94 had previously participated to the V59P2 study, and 25 were 24-month-old naïve subjects. They were distributed according to the following groups:

Group I (ACWY10): 14 subjects from group I of V59P2 study
Group II (CWY10): 20 subjects from group II of V59P2 study
Group III (A10CWY5): 24 subjects from group III of V59P2 study
Group IV (ACWY5): 17 subjects from group IV of V59P2 study
Group V (ACWY2.5): 19 subjects from group V of V59P2 study
Group VII (naïve; no MenACWY): 25 naïve children aged 24 months

The intention-to-treat and per-protocol population included a total of 119 and 118 subjects, respectively. Data from all subjects were included in the safety analyses.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria

Individuals were eligible for enrollment into this study if they were:

1. Male and female healthy children 22 to 24 months old inclusive, who had received one dose of the Novartis MenACWY in Novartis study V59P2 (groups I to V) at least 6 months earlier and whose parents or legal representatives had given written informed consent prior to entry into this study;

OR

1. Male and female healthy naïve children 24 months old (group VII), whose parents or legal representatives had given written informed consent prior to the study entry.
2. Available for all the visits scheduled in the study;
3. In good health as determined by:
   - Medical history;
   - Physical examination;
   - Clinical judgment of the investigator.

Exclusion criteria

An individual was not to be enrolled into the study if:

1. His/her parents or legal representatives were unwilling or unable to give written informed consent to participate in the study;
2. He/she had experienced within the previous 7 days significant acute or chronic infections requiring antiviral therapy or they had experienced fever of 38.5°C or higher within the previous 3 days;
3. He/she had received in the previous 15 days any systemic antibiotic treatment (EXCEPTION: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, etc.] might have been enrolled 7 days following the last dose);
4. He/she had any serious chronic disease such as cardiac, autoimmune disease, or insulin-dependent diabetes;
5. He/she had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
6. He/she had any condition, which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives;
7. His/her families were planning to leave the area of the study site before to the end of the study period;

8. He/she had received another vaccine within the previous 30 days or was expected to receive another vaccine during the study period;
9. He/she had received a live viral vaccine within the previous 60 days;
10. He/she had laboratory confirmed *N meningitidis* infection or a history of a previous disease potentially related to any meningococcal infection;
11. He/she had household contact and/or intimate exposure in the previous 30 days to an individual with ascertained *N meningitidis* serogroup A or C or W or Y disease;
12. Had a genetic anomaly (i.e., known cytogenic disorder);
13. He/she had ever been immunized with any meningococcal polysaccharide or conjugate vaccine (only for group VII);
14. He/she was known to have a bleeding diathesis or any condition that may be associated with a prolonged bleeding time;
15. He/she had received parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the previous 90 days.

Test product, dose, mode of administration, lot number:

One injection of a licensed tetravalent meningococcal ACWY polysaccharide vaccine (GSK MENCEVAX™ ACWY) was administered as challenge dose subcutaneously in the deltoid region to children previously vaccinated with one dose of the investigational Novartis MenACWY (group I-V).

One injection of the same vaccine was administered subcutaneously in the deltoid region to naïve children 24 months old (group VII).

The licensed vaccine contains 50 µg of plain polysaccharide from each of four meningococcal serogroups (A, C, W, and Y) in a single 0.5 mL dose.

Lot Number: N412A42B-1
Expiry date: April 2005

Name of Ingredients	Quantity per dose
Isolated product from each of groups A, C, Y, and W_{135}	50 µg
Lactose	(b) (4)
Water for injection (NaCl 0.9%)	(b) (4) mL

Duration of study:

Expected subject enrollment interval: approximately 8 weeks

Duration of individual subject's participation: 4 weeks

Total duration of study: approximately 12 weeks

Reference therapy, dose, mode of administration, lot number:

No reference vaccine was administered.

Criteria for evaluation:
Immunogenicity
The following serological assessment was considered for each serogroup for evaluation of **persistence of antibodies** (groups I to V: ACWY10, CWY10, A10CWY5, ACWY5, and ACWY2.5, respectively):

- Percentage of subjects with human serum bactericidal assay (hSBA) titer greater than or equal to 1:4 and to 1:8.

The following serological assessments were considered for each serogroup for evaluation of **immunological memory following a challenge dose of PS ACWY**:

- Percentage of subjects with hSBA titer greater than or equal to 1:4 and to ≥ 1:8;
- Geometric mean titer (GMT) ratio (GMR) for each vaccination group .

The following serological assessments were considered for each serogroup **for evaluation of primary immunogenicity following one dose of PS ACWY:**

- Percentage of subjects with hSBA titer greater than or equal to 1:4 and to 1:8.

Safety
Number of subjects with reported local and systemic reactions, as well as number of subjects with reported serious adverse events, and/or all adverse events up to day 7, and/or adverse events requiring a physician visit and/or resulting in premature withdrawal from the study, for each vaccination group.

Statistical Methods:
There was no statistical (null) hypothesis associated with the immunogenicity objective. All analyses were run descriptively.

Summary and Conclusions:
Immunogenicity results
Six-month persistence of the V59P2 antibody response to serogroups C, W, and Y, but not A, was demonstrated during the present study. Additionally, all V59P2 MenACWY vaccine groups, but not the naïve subjects group, exhibited a positive anamnestic (booster) response to all serogroups at 1 month after challenge with a PS ACWY vaccine.

For naïve subjects, no detectable antibody titers against any of the four serogroups were seen at baseline. By contrast, for primed subjects, persistence of antibody activity was detected against serogroups C (range = 25% to 45%), W (44% to 64%), and Y (57% to 81%), but not against serogroup A, before the PS ACWY challenge on day 1 of V59P2E1, at least 6 months after single immunization in study V59P2. Against serogroup A, one of 19 (5%) ACWY2.5 group V subjects had an hSBA titer greater than or equal to 1:4. No antibodies against serogroup A were noted in any other subject or group at the V59P2E1 prechallenge baseline.

Using the more conservative titer cutoff of hSBA greater than or equal to 1:8, 6-month persistence of antibody activity in response to V59P2 immunization was very similar to, although slightly lower than, that detected using the 1:4 titer cutoff.

Using GMTs and GMRs for assessment, conclusions about persistence of antibody response to single immunization of subjects previously enrolled in study V59P2 was very similar to that using the 1:4 and 1:8 titer cutoff. All subjects that were previously vaccinated in study V59P2 showed persistence against serogroups C (GMT range = 3.04 to 5.34), W (5.04 to 8.14), and Y (7.68 to 10), but not against serogroup A (2.0 to 2.14). For the naïve subjects group (group VII), no antibody activity in GMTs at V59P2E1 baseline was detected against any serogroup.

There was no apparent relationship between the vaccine groups or dosages of each antigen in study V59P2 and the persistence of the antibody response at least 6 months after the single V59P2 immunization.

Positive anamnestic (booster) responses were seen in each MenACWY vaccine group, and a low level of response was seen in the naïve subjects group. One month after the administration of a full dose of PS ACWY, a high percentage of subjects previously vaccinated with MenACWY attained hSBA titers greater than or equal to 1:4 against serogroups C, W, and Y (range: 94% to 100%), while 35% of subjects previously vaccinated with the CWY10 dose (group II) reached the 1:4 criterion against serogroup A, compared to results obtained at the prechallenge baseline. Only a small percentage of naive subjects reached the 1:4 titer (20% for serogroup A, 8% for serogroup C, 8% for serogroup W, and 32% for serogroup Y). Percentages of subjects reaching the more conservative hSBA titers of at least 1:8 were similar to those obtained using the 1:4 criterion. Day 29 GMTs in MenACWY vaccine groups ranged from 92 to 157 against serogroup A (CWY10 GMT = 5.04; naïve group GMT = 3.87), from 527 to 724 against serogroup C (CWY10 GMT = 854; naïve group = 2.25) from 293 to 572 against serogroup W (CWY10 GMT = 499; naïve group = 2.49), and 239 to 596 against serogroup Y (CWY10 GMT = 446; naïve group = 3.51).

Increases in hSBA titers from day 1 to day 29, represented by GMRs, were low for the naïve subjects (1.93-fold) and for the CWY10 group that received vaccine without the A component (2.52-fold), while GMRs for all other MenACWY vaccine groups ranged from 46-fold to 78-fold. Serogroup C GMRs of the primed groups ranged from 111-fold for the ACWY2.5 group to 207-fold for the A10CWY5 group (naïve group GMR = 1.12-fold). Serogroup W GMRs of the primed groups ranged from 36-fold for the ACWY10 group to 98-fold for the A10CWY5 group (naïve group GMR = 1.25-fold). Serogroup Y GMRs of primed groups ranged from 31-fold for the ACWY10 group to 65-fold for the ACWY5 group (naïve group GMR = 1.75-fold). Taken together and with the comparison to the naïve controls, these results suggest that a booster response was demonstrated against each of the four serogroups in toddlers after a single dose of any of the MenACWY formulations tested.

Total IgG against the four meningococcal serogroups, as measured by ELISA, were determined for the A10CWY5 group and the naïve subjects group who were enrolled in study V59P2E1 and who had both day 1 and day 29 results. At baseline, geometric mean concentrations (GMCs) against each of the four serogroups were lower for naïve subjects compared with the A10CWY5 group previously primed with MenACWY in study V59P2.

ELISA GMCs achieved after challenge with PS ACWY were higher for primed subjects (between 24 and 53) than for naïve subjects (between 3.43 and 12). In both primed and naïve groups, the highest GMCs were obtained against serogroup W-specific antibodies. GMRs for serogroups A, W, and Y increased to a greater extent in the A10CWY5 group compared to the naïve group. Against serogroup C, no major difference between primed and naive subjects was observed (GMR = 54 and 46, respectively).

Safety results

The reactogenicity profile of subjects previously vaccinated in V59P2 study (i.e., primed subjects) and of nonvaccinated subjects (i.e., naïve subjects) was similar.

No pain on injection was reported at any time during the study.

The percentage of subjects who experienced any sign of reactogenicity after a single challenge of PS ACWY vaccine was similar for primed and naïve subjects groups. Sixty-nine percent of primed subjects and 76% of the naïve subjects reported at least one symptom of reactogenicity.

No clinically significant differences in incidence of local, systemic, or other reactions were noted. The most frequent local reactions were tenderness (combined MenACWY = 48%; naïve = 56%) and erythema (combined MenACWY = 18%; naïve = 24%). The most frequent systemic reactions were irritability 24% and 24%, respectively), change in eating habits (6% and 28%), and sleepiness (16% and 12%). The incidence of other reactions was similar: use of analgesics or antipyretics was reported by 9% and 20% of primed and naïve subjects, and rectal temperature greater than or equal to 38.5°C was reported by 7% and 12% of subjects, respectively.

A single subject experienced a severe local reaction (cried upon movement of the injected limb at 6 hours after PS challenge: A10CWY5 vaccine group from V59P2 study). No erythema or induration greater than 25 mm was noted during the study.

No deaths were reported during the study. One SAE (tonsillitis in a naïve subject) was reported but was considered unrelated to PS ACWY challenge by the investigator. No premature withdrawals due to AEs and no AE-related dose reductions, interruptions, or delays were reported during the study.

A total of 41% and 48% of primed subjects and naïve subjects, respectively, reported at least one AE. The most frequently reported individual AEs, regardless of relationship to study vaccine, were otitis media (6% and 20% in primed and naïve groups, respectively), cough (7% and 12%), pyrexia (8% and 0%), rhinitis (5% and 8%), upper respiratory tract infection (5% and 4%), conjunctivitis (3% and 4%), and bronchitis (4% and 0%). All AEs were mild or moderate in intensity except a single event of severe constipation, which was considered not related to the study vaccine, 17 days after vaccine administration in a primed subject. There were no clinically significant differences in the incidence of individual AEs regardless of vaccine relationship.

Nine of 94 primed subjects (10%) and one of 25 naïve subjects (4%) reported at least one mild to moderate, transient AE that was considered possibly or probably related to study vaccine administration during study. The most frequently reported vaccine-related AEs were pyrexia and haematoma (2 subjects [2%] each) in the primed subjects group and vomiting, diarrhoea, and eating disorder, all reported by a single naïve

subject. Other vaccine-related AEs in both primed and naïve subjects were reported by a single subject.

Conclusions

Persistence of antibodies against serogroups C, W, and Y, but not serogroup A, was evident at 6 to 8 months after a single vaccination with different formulations of Novartis MenACWY in study V59P2.

After the administration of PS ACWY challenge, subjects who had previously received Novartis MenACWY showed a positive anamnestic (booster) response against any of the four serogroups, compared to the prechallenge baseline and to the naïve subjects group who received a full dose of PS ACWY.

It is important to note that, although no persistence to MenA was demonstrated, the PS ACWY challenge was consistent with the induction of memory to MenA. This was shown both by the near-universal response in those subjects with prior MenACWY (any formulation) but, more importantly, by the significantly higher responses to MenA when the PS probe was given to them compared to the naïve age-matched cohort.

The reactogenicity profile to PS ACWY for the subjects previously vaccinated in study V59P2 and for the naïve subjects were comparable. Most possibly/probably related AEs were mild, and none were severe. Only one SAE was reported during the study and was judged by the investigator as not related to PS ACWY administration.

In summary, this extension study showed that the formulations previously tested in the V59P2 study had significant antibody response as long as 6 months after the single MenACWY injection against C, W, and Y serogroups, but not the A serogroup and that this persistence elicited a significant increase in antibody titers when subjects were challenged with a PS ACWY vaccine. Polysaccharide ACWY challenge was well tolerated by both previously vaccinated and naïve subjects in the present study.

Table 2-1 Time and Events Schedule

Study Visit Day	1	Phone Call	Phone Call	29 (+7)
Visit	**1**			**2**
Days After Visit 1	**1**	**2 (+1)**	**7 (+1)**	**28-35**
Obtain informed consent	X			
Medical history	X			
Complete physical examination	X			X
Screen for inclusion/exclusion criteria	X			
Follow-up telephone call		X[b]	X[b]	
Blood draw for assays	X			X
Measure rectal temperature	X			
Immunization	X			
Injection site examination	X			X
Assess local/systemic reactions	X	X	X	X
Assess concomitant medications	X	X	X	X
Assess adverse events	X	X	X	X
Diary card review				X[a]
Complete study termination				X

X[a]: Collect diary card and reconcile with the data on the "Local and Systemic Reactions" CRF and information collected during the phone calls.
X[b]: Record date and comments (if applicable) on the "Compliance" CRF.

Table 2-2 Percentages of Subjects With Human SBA Titers Greater Than or Equal to 1:4 Before and One Month After Polysaccharide ACWY Challenge

Percentage of Subjects With Human SBA Titers ≥ 1:4 (95% CI)							
Serogroup	**(MenACWY formulation)**	**Group I (10-10-10-10 µg) ACWY10**	**Group II (0-10-10-10 µg) CWY10**	**Group III (10-5-5-5 µg) A10CWY5**	**Group IV (5-5-5-5 µg) ACWY5**	**Group V (2.5-2.5-2.5-2.5 µg) ACWY2.5**	**Group VII (naïve) no MenACWY**
		N = 14	N = 20	N = 24	N = 16	N = 19	N = 25
A	day 1 [a]	0 (0-23)	0 (0-17)	0 (0-14)	0 (0-21)	5 (0-26)	0 (0-14)
	day 29 [b]	100 (77-100)	35 (15-59)	100 (86-100)	94 (70-100)	100 (82-100)	20 (7-41)
C	day 1 [a]	43 (18-71)	45 (23-68)	29 (13-51)	25 (7-52)	37 (16-62)	0 |(0-14)
	day 29 [b]	100 (77-100)	100 (83-100)	100 (86-100)	94 (70-100)	100 (82-100)	8 (1-26)
W	day 1 [a]	64 (35-87)	45 (23-68)	58 (37-78)	44 (20-70)	53 (29-76)	0 (0-14)
	day 29 [b]	100 (77-100)	100 (83-100)	100 (86-100)	100 (79-100)	100 (82-100)	8 (1-26)
Y	day 1 [a]	57 (29-82)	60 (36-81)	67 (45-84)	81 (54-96)	68 (43-87)	0 (0-14)
	day 29 [b]	100 (77-100)	100 (83-100)	100 (86-100)	100 (79-100)	100 (82-100)	32 (15-54)

Source: Table 14.2.1.2

[a] Persistence 6 months after single immunization in study V59P2: day 1 results from serology samples obtained before PS ACWY challenge in study V59P2E1.

[b] Anamnestic (booster) response at 1 month after PS ACWY challenge in study V59P2E1.

CI = confidence interval, hSBA = human serum bactericidal assay

Table 2-3 Percentages of Subjects With Human SBA Titers Greater Than or Equal to 1:8 Before and One Month After Polysaccharide ACWY Challenge

Percentage hSBA ≥ 1:8 (95% CI)							
Serogroup	**(MenACWY formulation)**	**Group I (10-10-10-10 µg) ACWY10**	**Group II (0-10-10-10 µg) CWY10**	**Group III (10-5-5-5 µg) A10CWY5**	**Group IV (5-5-5-5 µg) ACWY5**	**Group V (2.5-2.5-2.5-2.5 µg) ACWY2.5**	**Group VII (naïve) no MenACWY**
		N = 14	N = 20	N = 24	N = 16	N = 19	N = 25
A	day 1 [a] V59P2E1	0 (0-23)	0 (0-17)	0 (0-14)	0 (0-21)	0 (0-18)	0 (0-14)
	day 29 [b] V59P2E1	93 (66-100)	35 (15-59)	100 (86-100)	88 (62-98)	95 (74-100)	20 (7-41)
C	day 1 [a] V59P2E1	36 (13-65)	40 (19-64)	21 (7-42)	19 (4-46)	32 (13-57)	0 (0-14)
	day 29 [b] V59P2E1	100 (77-100)	100 |(83-100)	100 (86-100)	94 (70-100)	100 (82-100)	4 (0-20)
W	day 1 [a] V59P2E1	50 (23-77)	35 (15-59)	42 (22-63)	31 (11-59)	53 (29-76)	0 (0-14)
	day 29 [b] V59P2E1	100 (77-100)	95 (75-100)	100 (86-100)	100 (79-100)	100 (82-100)	8 (1-26)
Y	day 1 [a] V59P2E1	50 (23-77)	55 (32-77)	54 (33-74)	50 (25-75)	37 (16-62)	0 (0-14)
	day 29 [b] V59P2E1	100 (77-100)	95 (75-100)	100 (86-100)	100 (79-100)	100 (82-100)	20 (7-41)

Source: Table 14.2.1.5

[a] Persistence 6 months after single immunization in study V59P2: day 1 results from serology samples obtained before PS ACWY challenge in study V59P2E1.

[b] Anamnestic (booster) response at 1 month after PS ACWY challenge in study V59P2E1.

CI = confidence interval, hSBA = human serum bactericidal assay.

Table 2-4 hSBA GMTs and GMRs Before and One Month After Polysaccharide ACWY Challenge

hSBA GMT and GMR (95% CI)							
Serogroup	**(MenACWY formulation)**	**Group I (10-10-10-10 µg) ACWY10**	**Group II (0-10-10-10 µg) CWY10**	**Group III (10-5-5-5 µg) A10CWY5**	**Group IV (5-5-5-5 µg) ACWY5**	**Group V (2.5-2.5-2.5-2.5 µg) ACWY2.5**	**Group VII (naïve) no MenACWY**
		N = 14	N = 20	N = 24	N = 16	N = 19	N = 25
A	day 1 [a]	2 (1.88-2.13)	2 (1.9-2.1)	2 (1.91-2.1)	2 (1.89-2.12)	2.14 (2.03-2.25)	2 (1.91-2.09)
	day 29 [b]	92 (43-197)	5.04 (2.67-9.52)	157 (88-280)	102 (50-208)	121 (63-233)	3.87 (2.19-6.83)
	day 29/ day 1	46 (22-98)	2.52 (1.34-4.74)	78 (44-139)	51 (25-104)	57 (30-108)	1.93 (1.1-3.4)
C	day 1 [a]	4.28 (2.59-7.08)	5.34 (3.5-8.13)	3.5 (2.38-5.13)	3.04 (1.9-4.86)	4.76 (3.09-7.32)	2 (1.37-2.91)
	day 29 [b]	721 (389-1334)	854 (510-1430)	724 (452-1159	546 (307-971)	527 (310-893)	2.25 (1.42-3.56)
	day 29/ day 1	168 (89-317)	160 (94-272)	207 (128-336)	180 (99-325)	111 (64-191)	1.12 (0.7-1.8)
W	day 1 [a]	8.14 (4.47-15)	5.77 (3.49-9.52)	5.83 (3.69-9.21)	5.04 (2.88-8.83)	7.25 (4.33-12)	2 (1.28-3.13)
	day 29 [b]	293 (143-603)	499 (273-912)	572 (330-992)	449 (229-881)	469 (253-871)	2.49 (1.45-4.27)
	day 29/ day 1	36 (17-75)	87 (47-161)	98 (56-173)	89 (45-178)	65 (34-122)	1.25 (0.72-2.17)
Y	day 1 [a]	7.68 (4.03-15)	8.7 (5.07-15)	10 (6.21-17)	8.54 (4.67-16)	7.75 (4.45-13)	2 (1.23-3.24)
	day 29 [b]	239 (109-527)	446 (230-863)	596 (326-1090)	554 (264-1159)	337 (171-665)	3.51 (1.94-6.33)
	day 29/ day 1	31 (14-68)	51 (27-99)	59 (32-107)	65 (31-135)	44 (22-85)	1.75 (0.97-3.16)

Source: Table 14.2.1.8

[a] Persistence 6 months after single immunization in study V59P2: day 1 results from serology samples obtained before PS ACWY challenge in study V59P2E1.

[b] Anamnestic (booster) response at 1 month after PS ACWY challenge in study V59P2E1.

GMT = geometric mean titer, GMR = geometric mean ratio, CI = confidence interval

Table 2-5 Overview of Reactogenicity

Any sign of reactogenicity	Group I-V from V59P2 N = 94		Group VII (naïve) N = 25	
	Subjects n (%)		Subjects n (%)	
	All reactions	Severe reactions	All reactions	Severe reactions
	65 (69%)	na	19 (76%)	na
Local reactions				
Any local reaction	49 (52%)		15 (60%)	
• Tenderness	45 (48%)	1 (1%)	14 (56%)	0
• Erythema	17 (18%)	0	6 (24%)	0
• Induration	0	0	3 (12%)	0
Systemic reactions				
Any systemic reaction	36 (38%)	na	12 (48%)	na
• Change in eating habits	6 (6%)	na	7 (28%)	na
• Sleepiness	15 (16%)	na	3 (12%)	na
• Irritability	23 (24%)	na	6 (24%)	na
• Vomiting	3 (3%)	na	2 (8%)	na
• Diarrhea	5 (5%)	na	1 (4%)	na
• Persistent crying	0	na	0	na
• Oral temp ≥ 38.5°C	7 (7%)	na	3 (12%)	na
Other reactions				
Any other reaction	8 (9%)	na	5 (20%)	na
• Rectal temperature ≥ 38.5°C	7 (7%)	na	3 (12%)	na
• Analgesics/ antipyretics	8 (9%)	na	5 (20%)	na

Source: Tables 14.3.1.1.2 and 14.3.1.1.3.

Table 2-6 Treatment-Emergent Adverse Events

MedDRA SOC / -- Preferred Term	Group I-V N = 94 n (%)			Group VII (naïve) N = 25 n (%)		
	All [a]	All Severe [b]	Vaccine-related [c]	All [a]	All Severe [b]	Vaccine-related [c]
Any Adverse Event	**39 (41%)**	**1 (1%)**	**9 (10%)**	**12 (48%)**	**0**	**1 (4%)**
Infections & Infestations	**24 (26%)**	**0**	**2 (2%)**	**9 (36%)**	**0**	**0**
-- Otitis media	6 (6%)	0	0	5 (20%)	0	0
-- Rhinitis	5 (5%)	0	0	2 (8%)	0	0
-- Upper resp. tract inf.	5 (5%)	0	0	1 (4%)	0	0
-- Bronchitis	4 (4%)	0	1 (1%)	0	0	0
-- Respiratory tract inf.	3 (3%)	0	1 (1%)	0	0	0
-- Gastroenteritis	2 (2%)	0	1 (1%)	0	0	0
-- Ear infection	1 (1%)	0	1 (1%)	0	0	0
Gen. Disorders & Admin.Site Cond.	**9 (10%)**	**0**	**2 (2%)**	**1 (4%)**	**0**	**0**
-- Pyrexia	8 (9%)	0	2 (2%)	0	0	0
-- Irritability	2 (2%)	0	1 (1%)	1 (4%)	0	0
Resp., Thoracic, & Mediastinal Disorders	**7 (7%)**	**0**	**0**	**3 (12%)**	**0**	**0**
-- Cough	7 (7%)	0	0	3 (12%)	0	0
Eye Disorders	**4 (4%)**	**0**	**2 (2%)**	**1 (4%)**	**0**	**0**
-- Conjunctivitis	3 (3%)	0	1 (1%)	1 (4%)	0	0
-- Eyelid oedema	1 (1%)	0	1 (1%)	0	0	0
Gastrointestinal Disorders	**3 (3%)**	**1 (1%)**	**2 (2%)**	**2 (8%)**	**0**	**1 (4%)**
-- Abdominal pain	1 (1%)	0	1 (1%)	0	0	0
-- Constipation	1 (1%)	1 (1%)	0	0	0	0
-- Diarrhoea	0	0	0	1 (4%)	0	1 (4%)
-- Vomiting	2 (2%)	0	1 (1%)	1 (1%)	0	1 (1%)
Psychiatric Disorders	**3 (3%)**	**0**	**2 (2%)**	**1 (4%)**	**0**	**1 (4%)**
-- Eating disorder	2 (2%)	0	1 (1%)	1 (4%)	0	1 (1%)
-- Sleep disorder	1 (1%)	0	1 (1%)	0	0	0
Nervous System Disorders	**2 (2%)**	**0**	**1 (1%)**	**1 (4%)**	**0**	**0**
-- Somnolence	2 (2%)	0	1 (1%)	0	0	0
Skin & Subcut. Tissue Disorders	**1 (1%)**	**0**	**0**	**2 (8%)**	**0**	**0**
Vascular Disorders	**2 (2%)**	**0**	**2 (2%)**	**0**	**0**	**0**
-- Haematoma	2 (2%)	0	2 (2%)	0	0	0

Source: Table 14.3.1.1.11, 14.3.1.1.12, and 14.3.1.1.14. Subjects may be represented more than once; individual AE totals may not sum to system-organ-class totals.

Criteria for inclusion in table:

[a] 5% or greater AE incidence in either group; **OR**

[b] AE is severe in either group; **OR**

[c] AE is possibly or probably related to study vaccine, according to investigator, in either group.

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number:** V59P2E2	

Title of study: A Phase II, Open-label, Controlled, Single-Center Study to Evaluate the Immune Response Following One Dose of a Licensed Meningococcal ACWY Polysaccharide Vaccine 12 Months After One or Two Doses of Chiron Meningococcal ACWY Conjugate Vaccine (As Part of V59P2 study)

Protocol number: V59P2E2

Investigators: Prof. Timo Vesikari, MD

Study centers: University of Tampere Medical School, 33014 Tampere, Finland

Publication (reference): none

Study period: 31 MAY 04 to 01 NOV 04	**Phase of development:** Phase 2

Objectives:

Immunogenicity Objectives

- To evaluate the persistence of antibodies to *N meningitidis* serogroups ACWY at least 12 months after vaccination with one dose of Novartis MenACWY conjugate vaccine;
- To evaluate the persistence of antibodies to *N meningitidis* serogroups ACWY at least 12 months after vaccination with two doses of Novartis MenACWY conjugate vaccine;
- To evaluate the anamnestic response to *N meningitidis* serogroups ACWY after challenge with one dose of a licensed PS vaccine at least 12 months after vaccination with one dose of Novartis MenACWY conjugate vaccine as compared to the immunological response of naïve subjects receiving one dose of the same licensed polysaccharide (PS) vaccine;
- To evaluate the anamnestic response to *N meningitidis* serogroups ACWY after challenge with one dose of a licensed PS vaccine at least 12 months after vaccination with two doses of Novartis MenACWY conjugate vaccine as compared to the immunological response of naïve subjects receiving one dose of the same licensed PS vaccine.

Safety Objectives

- To monitor the safety of all study subjects during the study period.

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number:** V59P2E2	

Methodology:

This was a phase 2, open-label, controlled, single-center study. Healthy children who previously participated in Novartis study V59P2 in Finland and aged 24 to 28 months were enrolled in this study to evaluate the persistence of antibodies at approximately 12 months after vaccination with one or two doses of different formulations of Novartis MenACWY conjugate vaccine (Groups I, III, IV, and V of study V59P2).

These children were also challenged with one dose of a licensed PS vaccine to assess induction of immunological memory. In addition, a group of naïve children aged 24 to 28 months received one dose of a licensed PS vaccine (Group VII of the current study).

V59P2	**V59P2E2**		
		Visit 1[a]	**Visit 2[b]**
Conj Group Men A-C-W-Y µg	**PS Group Men A-C-W-Y 50-50-50-50 µg**	**Blood Draw/PS N**	**Blood Draw N**
I 10-10-10-10	I (ACWY10)	60	60
III 10-5-5-5	III (A10CWY5)	60	60
IV 5-5-5-5	IV (ACWY5)	60	60
V 2.5-2.5-2.5-2.5	V (ACWY2.5)	60	60
	VII (naive subjects)	60	60
Total Number		300	300

[a] 360-420 days after V59P2 study visit 1
[b] 43-58 days after visit 1 (current study)

Subjects were checked to ensure they were in good health and met all inclusion criteria and no exclusion criteria. Medical history was obtained and a physical examination was performed.

At visit 1 (360-420 days after visit 1 of study V59P2), a blood sample was taken, and a PS vaccine was administered subcutaneously (SC) in the deltoid region.

At visit 2 (43-58 days after visit 1 of the current study), a blood sample was obtained from all vaccinated subjects.

All subjects remained in the clinic for 30 minutes after vaccine administration to monitor for any hypersensitivity reactions and other adverse events (AEs). Their parents/legal representatives were then instructed to complete a diary card to describe local reactions (tenderness, erythema, induration), systemic reactions (change in eating habits, sleepiness, irritability, vomiting, diarrhea, persistent crying lasting more than 3

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number:** V59P2E2	

hours), analgesic or antipyretic use, and to record rectal temperature measurements daily for 7 days following vaccination. A telephone call was made to check for the subject's status on the third and eighth day after vaccination. Diary cards were collected at the study termination visit (visit 2).

Number of subjects (planned and analyzed):

Approximately 240 children from the V59P2 study who previously received one or two doses of the Novartis investigational MenACWY conjugate vaccines at least 12 months earlier were planned to participate in the current study (Groups I, III, IV, and V consisted of 60 subjects each). In addition, approximately 60 naïve children aged 24 to 28 months (Group VII) were planned to receive one dose of the PS vaccine.

A total of 244 subjects were enrolled in this study: 237 of the 244 subjects received a single dose of licensed PS vaccine (including 175 subjects with previous Novartis MenACWY vaccination and 62 naïve subjects).

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria

Individuals eligible for enrollment into this study were:

1a. male and female healthy children 24 to 28 months old who had received one or two doses of the Novartis MenACWY conjugate vaccine in Novartis study V59P2 (Groups I, III, IV, and V) at least 12 months earlier and whose parents or legal representative had given written informed consent prior to entry of the subject into this study;

OR

1b. male and female healthy children 24 to 28 months old (Group VII), whose parents or legal representatives had given written informed consent prior to entry of the subject into the study;

2. available for all the visits scheduled in the study;

3. in good health as determined by:
   - medical history;
   - physical examination;
   - clinical judgment of the investigator;

4. male and female healthy children who had not participated in the V59P2E1 extension trial.

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number:** V59P2E2	

Exclusion criteria

An individual was not to be enrolled into the study if:

1. his/her parents or legal representatives were unwilling or unable to give written informed consent for the subject to participate in the study;
2. he/she had experienced significant acute or chronic infections requiring antiviral therapy within 7 days prior to enrollment or they had experienced fever ≥ 38.5°C within 3 days prior to enrollment;
3. he/she had received any systemic antibiotic treatment in the 15 days prior to enrollment (exception: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, etc.] might have been enrolled 7 days following the last dose);
4. he/she had any serious chronic disease such as cardiac, autoimmune disease, or insulin-dependent diabetes;
5. he/she had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
6. he/she had any condition which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives;
7. his/her families were planning to leave the area of the study site before the end of the study period;
8. he/she had received another vaccine within 30 days prior to enrollment or expected to receive another vaccine during the 43- to 58-day study period;
9. he/she had received a live viral vaccine within 60 days prior to enrollment;
10. he/she had laboratory confirmed *N meningitidis* infection or a history of a previous disease potentially related to any meningococcal infection;
11. he/she had household contact and/or intimate exposure in the previous 30 days to an individual with ascertained *N meningitidis* serogroup A or C or W or Y disease;
12. he/she had a genetic anomaly (i.e., known cytogenic disorder);
13. he/she had ever been immunized with any meningococcal polysaccharide or conjugate vaccine (only for Group VII);
14. he/she was known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

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15. he/she had received parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 90 days prior to enrollment.

Test product, dose, mode of administration, lot number:

One injection of a licensed tetravalent meningococcal ACWY PS vaccine (GSK Mencevax™* ACWY, batch number: N412A42B-1) was administered as a challenge dose SC in the deltoid region to children previously vaccinated with one or two doses of the investigational Novartis MenACWY conjugate vaccine.

One injection of the same vaccine was to be administered SC in the deltoid region to naïve children 24 to 28 months old.

The licensed vaccine contained 50 µg of plain polysaccharide from each of four meningococcal serogroups (A, C, W, and Y) in a single 0.5 mL dose.

Duration of study: Each subject participated in the study for 43 to 58 days (until visit 2). Each subject received a single injection of study vaccine on day 1 and returned to the clinic nearly 2 months later for postvaccination assessments.

Reference therapy, dose, mode of administration, lot number:

No reference vaccine was to be administered.

* Mencevax is a registered trademark of GlaxoSmithKline

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Criteria for evaluation:

Immunogenicity

Serum bactericidal activity (SBA) was measured for each serogroup in the presence of human complement (hSBA) and then expressed as geometric mean titer (GMT) and percentage of subjects with hSBA titer ≥ 1:4 (% ≥ 1:4) and ≥ 1:8 (% ≥ 1:8).

Safety

Measures of safety and reactogenicity included data from observed local reactions and systemic reactions.

These data were collected together with rectal temperature, analgesic or antipyretic medication use, and all other adverse events during the first 7 days after the injection, including the day of vaccination (study days 1 through 7). Serious adverse events (SAE) and/or adverse events necessitating a physician's visit and/or resulting in the subject's premature withdrawal from the study were collected throughout the study.

Statistical methods:

There was no statistical (null) hypothesis associated with the immunogenicity objective. All analyses were run descriptively.

Statistical power considerations:

Assuming a total of approximately 160 evaluable subjects (40 subjects in each of the study vaccine groups I, III, IV, and V who received only one dose) for evaluation of persistency of antibodies (measured by the percentage of subjects with SBA ≥ 1:4) at least 12 months after one dose of Novartis MenACWY conjugate vaccine, the precision afforded with a sample size of 40 subjects, as measured by the 95% confidence interval (CI), depended on the underlying percentage of responders as follows:

Underlying Response (%)	95% CI (%)
20	9 – 36
30	17 – 47
40	25 – 57
50	34 – 66
60	43 – 75
70	54 – 83
80	64 – 91

To assess the memory response at least 12 months after one dose of Novartis MenACWY conjugate vaccine, hSBA GMTs for all serogroups (A, C, W, or Y) were to

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be evaluated separately for each study group I, III, IV, and V, and compared to the memory response of naïve subjects in group VII. Assuming approximately 100 subjects (children) evaluable for the memory response assessment (40 in any Group I to V and 60 in Group VII), there was 90% power to detect a 2.5-fold increase in hSBA GMTs for any of the four serogroups in any Group I, III, IV, and V over Group VII (a difference of $\log_{10}$ [2.5] = 0.398 in the $\log_{10}$ hSBA GMTs). There were currently no data on hSBA GMTs after one challenge dose of PS in children previously vaccinated with Novartis MenACWY conjugate vaccine. Power calculations were derived from previous data on the antibody response (SBA) after one dose of PS vaccine (Novartis study: V14P7T) in toddlers who were vaccinated 6 months earlier with one dose of either Men C or hepatitis A vaccine. The power calculations were based on a two-sided, two-sample, *t* test comparing two means using a 5% level of significance and assuming a common standard deviation of the $\log_{10}$ titers = 0.59 (80% CI for standard deviation of 0.49 to 0.59). The power calculations were not adjusted for the statistical tests performed for the four components.

Summary and Conclusions:

Seven of the 244 subjects enrolled in this study were not treated and were excluded from the safety dataset (the parents or legal representative of three subjects signed the informed consent form but withdrew the subject from participation prior to vaccination; four additional subjects were not treated because they did not fulfill the entrance criteria). Thus the safety dataset included 237 subjects (175 subjects with previous MenACWY vaccination and 62 naïve subjects). Three subjects developed withdrawal criteria or received an incorrect dose and were excluded from the PP population, immunogenicity after one dose of PS vaccine, i.e., the PP population, immunogenicity after one dose of PS vaccine consisted of 234 subjects (173 subjects with previous MenACWY vaccination and 61 naïve subjects). The sample size for each treatment group is given below.

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Dataset	**ACWY10 (N=43)**	**A10CWY5 (N=44)**	**ACWY5 (N=44)**	**ACWY2.5 (N=47)**	**Naïve Subjects (N=66)**
Safety subjects per group: n	42	44	43	46	62
MITT persistence at 12 months subjects per group: n	42	44	43	46	62
PP subjects for 1 month analysis per group: n	42	44	43	46	62
MITT PS challenge subjects per group: n	42	44	43	46	62
PP subjects for PS challenge per group: n	42	44	42	45	61

In the all-enrolled dataset, subjects were 24 to 29 months old; the average age was similar among the groups (range 25.6 to 26.6 months). Slightly more male subjects were included in all groups, ranging from a male:female ratio of 52%:48% in the A10CWY5 group to 63%:37% in the ACWY10 group. Nearly all subjects were Caucasian (98% to 100%). Body weights ranged from 9.0 to 20.3 kg, and mean body weights were similar among groups, ranging from 13.10 kg (naïve) to 13.73 kg (ACWY10).

Immunogenicity results

Persistence

Responder Rate (hSBA titer ≥ 1:4 and ≥ 1:8)

For serogroup A, the responder rates (i.e., percentages of subjects with hSBA titer ≥ 1:4) were low at 12 months after vaccination with one dose of different MenACWY vaccines, (0%, 7%, 4%, and 3%), but slightly higher after two doses of MenACWY (0%, 36%, 12%, and 18% for the ACWY10, A10CWY5, ACWY5, and ACWY2.5 groups, respectively).

Higher responder rates were observed for the other serogroups:

- for serogroup C, the percentages of responders ranged from 10% (ACWY10, A10CWY5, ACWY2.5) to 15% (ACWY5) after one dose of the different MenACWY vaccines and from 29% (A10CWY5, ACWY5) to 47% (ACWY2.5) after two doses;
- for serogroup W, the percentages of responders ranged from 27% (A10CWY5) to 50% (ACWY5) after one dose and from 29% (ACWY5) to 82% (ACWY2.5) after

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two doses, and

- for serogroup Y, the percentages of responders ranged from 46% (ACWY5) to 48% (ACWY2.5) after one dose and from 53% (ACWY5) to 88% (ACWY2.5) after two doses of different MenACWY vaccines.

In general, persistence was higher after previous administration of two doses of MenACWY compared to one dose. It should be noted that the sample size was low (26 to 30 subjects per group in the groups of subjects who received one dose and 12 to 17 subjects per group in the groups who received two doses).

Using hSBA titer ≥ 1:8 as the responder criterion, the percentages of responders were generally lower, but the overall results were similar to the responder rate ≥ 1:4.

Geometric Mean hSBA Titers

At 12 months after vaccination with different MenACWY vaccines, the geometric mean hSBA titers were low against serogroup A (from 2 to 2.25 after one dose and from 2 to 3.38 after two doses of different MenACWY vaccines). The lowest mean was always observed in the ACWY10 group and the highest mean GMT in the A10CWY5 group.

Higher GMT values were observed for the other serogroups:

- for serogroup C, GMT ranged from 2.36 (ACWY10 group) to 2.52 (A10CWY5 group) after one dose of vaccine and from 3.73 (ACWY10 group) to 6.03 (ACWY2.5 group); individual values varied between 2 and 98;
- for serogroup W, GMT ranged from 3.22 (A10CWY5 group) to 6.56 (ACWY5 group) after one dose of vaccine and from 4.22 (ACWY10 group) to 11 (ACWY2.5 group); individual values varied between 2 and 177;
- for serogroup Y GMT ranged from 4.81 (ACWY10 group) to 6.23 (ACWY2.5 group) after one dose of vaccine and from 7.31 (ACWY5 group) to 13 (ACWY2.5 group); individual values varied between 2 and 658.

Due to high variability of the GMT, the 95% CIs generally overlapped among all MenACWY groups. Most one-dose and two-dose MenACWY GMTs were greater than the baseline GMTs for the PS naïve subjects group.

Challenge With One Dose of PS Vaccine

Further objectives of the study were to evaluate the anamnestic response to *N meningitidis* serogroups A, C, W, and Y after challenge with one dose of a licensed PS vaccine at least 12 months after vaccination with one or two doses of MenACWY vaccine compared to the immunological response of naïve subjects who received one

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dose of the same licensed PS vaccine.

Responder Rate

hSBA Titers ≥ 1:4

Nearly all subjects who had a challenge with licensed PS vaccine 12 months after vaccination with one or two doses of MenACWY were responders (hSBA titer ≥ 1:4). For subjects who received one dose of MenACWY, the responder rates were very high:

- between 90% (A10CWY5) and 100% (ACWY2.5) for serogroup A,
- between 96% (ACWY5) and 100% (all other treatments) for serogroup C,
- between 96% (ACWY5) and 100% (A10CWY5, ACWY2.5) for serogroup W, and
- between 96% (ACWY5) and 100% (A10CWY5, ACWY2.5) for serogroup Y.

For subjects who received two doses of MenACWY, the responder rates were also very high:

- 100% for all groups for serogroups A, C, and Y, and
- between 94% (ACWY5, ACWY2.5) and 100% (ACWY10, A10CWY5) for serogroup W.

In contrast, the responder rates were lower in naïve subjects who received one dose of licensed PS vaccine: 34%, 18%, 13%, and 44% of the subjects were responders for serogroups A, C, W, and Y, respectively.

hSBA Titers ≥ 1:8

For subjects who received one dose of MenACWY, the responder rates (hSBA titer ≥ 1:8) were:

- between 83% (A10CWY5) and 100% (ACWY2.5) for serogroup A,
- between 92% (ACWY5) and 100% (all other treatments) for serogroup C,
- between 93% (ACWY10) and 100% (A10CWY5, ACWY2.5) for serogroup W, and
- between 96% (ACWY5) and 100% (A10CWY5, ACWY2.5) for serogroup Y.

For subjects who received two doses of MenACWY, the responder rates were:

- 100% for all groups against serogroups A and C,
- between 94% (ACWY5, ACWY2.5) and 100% (ACWY10, A10CWY5) against serogroup W, and

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- between 92% (ACWY10) and 100% (A10CWY5, ACWY5) against serogroup Y.

The responder rates in naïve subjects were 25%, 11%, 10%, and 38% for serogroups A, C, W, and Y, respectively. The 95% CI for the naïve subjects did not overlap with any of the 95% CIs for the groups that received previous MenACWY vaccination, indicating statistically significant differences between the group of naïve subjects and all vaccine groups with previous Novartis MenACWY vaccination.

hSBA Geometric Mean Titers

Subjects who received a challenge with licensed PS vaccine 12 months after vaccination with one or two doses of MenACWY showed a remarkable increase in GMT from day 1 before challenge to 44 days after challenge.

The increase was lowest for serogroup A (28- to 46-fold increase after one dose of MenACWY vaccines and 32- to 73-fold increase after two doses of MenACWY vaccines). The geometric mean ratios (GMR = GMT day 44/GMT day 1) for the other serogroups were higher:

For subjects who received one dose of MenACWY, the GMRs ranged:

- from 212 (ACWY10) to 242 (A10CWY5) for serogroup C,
- from 63 (ACWY10) to 177 (A10CWY5) for serogroup W, and
- from 51 (ACWY10) to 122 (A10CWY5) for serogroup Y.

For subjects who received two doses of MenACWY, GMRs ranged:

- from 101 (ACWY5) to 178 (A10CWY5) for serogroup C,
- from 92 (ACWY5) to 161 (ACWY10) for serogroup W, and
- from 40 (ACWY10) to 79 (ACWY2.5) for serogroup Y.

Administration of licensed PS vaccine to naïve subjects resulted in 1.99-, 1.43-, 1.35-, and 3.22-fold increase in GMT in response to serogroups A, C, W, and Y, respectively, from day 1 to day 44.

Safety results

The percentages of subjects who experienced any sign of reactogenicity after a single vaccination with licensed PS vaccine were similar for all treatment groups: 64%, 66%, 65%, and 70% of the subjects in groups ACWY10, A10WCY5, ACWY5, and ACWY2.5, respectively; 73% of the naïve subjects reported at least one symptom of reactogenicity.

Injection site reactions, mainly tenderness and erythema, were reported by 50%, 57%,

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56%, and 52% of the subjects in ACWY10, A10WCY5, ACWY5, and ACWY2.5 groups, respectively, and by 65% of the naïve subjects. Systemic reactions were observed in 29%, 27%, 44%, and 39% of the subjects in ACWY10, A10WCY5, ACWY5, and ACWY2.5 groups, respectively, and in 31% of the naïve subjects. Other reactions were less frequently observed: in 0% to 7% of the subjects previously vaccinated with MenACWY and in 8% of the naïve subjects. There were no noteworthy differences between subjects previously vaccinated with MenACWY and naïve subjects.

Three subjects experienced an SAE: one subject in the ACWY10 group (anaphylactic shock, considered possibly drug related), one subject in the ACWY5 group (pyelonephritis) and one naïve subject (chronic bronchitis), both considered unrelated to vaccine administration.

At least one AE was experienced by 21%, 30%, 37%, and 35% of the subjects in the ACWY10, A10CWY5, ACWY5, and ACWY2.5 groups, respectively, and by 42% of the naïve subjects, after vaccination with one dose of licensed PS vaccine.

The most frequently reported AEs were infections or infestations followed by injuries or poisoning. The incidence of individual AEs, regardless of causality, was highest for rhinitis (5%, 2%, 12%, and 2% in the ACWY10, A10CWY5, ACWY5, and ACWY2.5 groups, respectively, and 8% in the group of naïve subjects) and otitis media (2%, 7%, 2%, and 9% in the ACWY10, A10CWY5, ACWY5, and ACWY2.5 groups, respectively, and 3% in the group of naïve subjects).

Most AEs were of mild to moderate intensity. Only the subjects with SAEs had AEs of severe intensity. Most AEs were considered to be unrelated to the study vaccine; 2% (ACWY10, ACWY5, and naïve subjects) and 7% and 9% (A10CWY5, ACWY2.5) of the subjects experienced AEs that were considered by the investigator to be possibly or probably related to study vaccines.

Conclusions

Persistence

- Persistence (percentage of responders with hSBA titer ≥ 1:4) was low for serogroup A and higher for the other serogroups. In general, the responder rate was higher after previous administration of two doses of MenACWY compared to one dose.
- Generally higher GMT values were obtained after previous administration of two doses of MenACWY compared to one dose.

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Challenge With One Dose of PS Vaccine

- The anamnestic response was high with 90% to100% responders (hSBA titer ≥ 1:4) for all serogroups and independent of the number and the composition of the previous administrations of MenACWY vaccine. In naïve subjects, who received one dose of licensed PS vaccine, the responder rate varied between 13% and 44% for the different serogroups.
- After challenge, a remarkable increase in GMT was observed for all serogroups and for all MenACWY treatment groups (40- to 242-fold). In naïve subjects, an approximate 2- to 3-fold increase in GMT was seen.

Safety

A single dose of licensed PS vaccine was well tolerated. There were no differences with regard to local or systemic reactions or other adverse events between subjects with previous vaccination with Novartis MenACWY vaccines and naïve subjects.

Table 2.0-1 Time and Events Schedule

STUDY VISIT DAY	**1**	**Phone Call☎**	**Phone Call☎**	**44**
VISIT	**1**			**2**
STUDY DAY	**1**	**3 (+1)**	**8 (+1)**	**43-58 days after visit 1**
Obtain informed consent	X			
Medical history	X			
Complete physical examination	X			X
Screen for inclusion/exclusion criteria	X			
Follow-up telephone call		X[b]	X[b]	
Blood draw for assays	X			X
Measure rectal temperature	X			
Immunization	X			
Injection-site examination	X			X
Assess local/systemic reactions	X	X	X	X
Assess concomitant medications	X	X	X	X
Assess adverse events	X	X	X	X
Diary card review				X[a]
Complete study termination				X

[a] Collect diary card and reconcile with the data on the Local and Systemic Reaction CRF and information collected during the phone calls

[b] Record date and comments (if applicable) on the Compliance CRF

Table 2.0-2 Percentage of Responders (hSBA Titers ≥ 1:4) at 12 Months After Vaccination With One or Two Doses of Novartis MenACWY Vaccine

Sero-group	Day 1 V59P2E2	ACWY10		A10CWY5		ACWY5		ACWY2.5	
		1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	1 dose	2 doses
A	n (%) ≥ 1:4	0 (0)	0 (0)	2 (7)	5 (36)	1 (4)	2 (12)	1 (3)	3 (18)
	95% CI (%)	0-12	0-26	1-22	13-65	0.097-20	1-36	0.087-18	4-43
	N	30	12	30	14	26	17	29	17
C	n (%) ≥ 1:4	3 (10)	5 (42)	3 (10)	4 (29)	4 (15)	5 (29)	3 (10)	8 (47)
	95% CI (%)	2-27	15-72	2-27	8-58	4-35	10-56	2-27	23-72
	N	30	12	30	14	26	17	29	17
W	n (%) ≥ 1:4	12 (41)	5 (42)	8 (27)	9 (64)	13 (50)	5 (29)	12 (41)	14 (82)
	95% CI (%)	24-61	15-72	12-46	35-87	30-70	10-56	24-61	57-96
	N	29	12	30	14	26	17	29	17
Y	n (%) ≥ 1:4	14 (47)	7 (58)	14 (47)	10 (71)	12 (46)	9 (53)	14 (48)	15 (88)
	95% CI (%)	28-66	28-85	28-66	42-92	27-67	28-77	29-67	64-99
	N	30	12	30	14	26	17	29	17

Source: [Table 11.4.1.1-1] Table 14.2.1.1. Individual subject results: Appendix 16.2.6.1.

Table 2.0-3 Percentage of Responders (hSBA Titers ≥ 1:4) After Challenge With One Dose of Licensed PS Vaccine

Day	hSBA	ACWY10		A10CWY5		ACWY5		ACWY2.5		Naive
		1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	
Serogroup A										
1	n (%) ≥ 1:4	0 (0)	0 (0)	2 (7)	5 (36)	1 (4)	2 (12)	1 (4)	3 (18)	0 (0)
	95% CI (%)	0-12	0-26	1-22	13-65	0-20	1-36	0.09-18	4-43	0-6
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:4	28 (93)	12 (100)	27 (90)	14 (100)	24 (96)	17 (100)	28 (100)	17 (100)	21 (34)
	95% CI (%)	78-99	74-100	73-98	77-100	80-100	80-100	88-100	80-100	23-48
	N	30	12	30	14	25	17	28	17	61
Serogroup C										
1	n (%) ≥ 1:4	3 (10)	5 (42)	3 (10)	4 (29)	4 (16)	5 (29)	3 (11)	8 (47)	1 (2)
	95% CI (%)	2-27	15-72	2-27	8-58	5-36	10-56	2-28	23-72	0.041-9
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:4	30 (100)	12 (100)	30 (100)	14 (100)	24 (96)	17 (100)	28 (100)	17 (100)	11 (18)
	95% CI (%)	88-100	74-100	88-100	77-100	80-100	80-100	88-100	80-100	9-30
	N	30	12	30	14	25	17	28	17	61
Serogroup W										
1	n (%) ≥ 1:4	12 (41)	5 (42)	8 (27)	9 (64)	13 (52)	5 (29)	11 (39)	14 (82)	1 (2)
	95% CI (%)	24-61	15-72	12-46	35-87	31-72	10-56	22-59	57-96	0.041-9
	N	29	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:4	28 (97)	12 (100)	30 (100)	14 (100)	24 (96)	16 (94)	28 (100)	16 (94)	8 (13)
	95% CI (%)	82-100	74-100	88-100	77-100	80-100	71-100	88-100	71-100	6-24
	N	29	12	30	14	25	17	28	17	61
Serogroup Y										
1	n (%) ≥ 1:4	14 (47)	7 (58)	14 (47)	10 (71)	12 (48)	9 (53)	13 (46)	15 (88)	1 (2)
	95% CI (%)	28-66	28-85	28-66	42-92	28-69	28-77	28-66	64-99	0.041-9
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:4	29 (97)	12 (100)	30 (100)	14 (100)	24 (96)	17 (100)	28 (100)	17 (100)	27 (44)
	95% CI (%)	83-100	74-100	88-100	77-100	80-100	80-100	88-100	80-100	32-58
	N	30	12	30	14	25	17	28	17	61

Source: [Table 11.4.1.2-1] Table 14.2.1.2. Individual subject results: Appendix 16.2.6.1.

Table 2.0-4 Percentage of Responders (hSBA Titers ≥ 1:8) After Challenge With One Dose of Licensed PS Vaccine

Day	hSBA	ACWY10		A10CWY5		ACWY5		ACWY2.5		Naive
		1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	
Serogroup A										
1	n (%) ≥ 1:8	0 (0)	0 (0)	2 (7)	3 (21)	1 (4)	2 (12)	1 (4)	1 (6)	0 (0)
	95% CI (%)	0-12	0-26	1-22	5-51	0-20	1-36	0.09-18	0-29	0-6
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:8	27 (90)	12 (100)	25 (83)	14 (100)	23 (92)	17 (100)	28 (100)	17 (100)	15 (25)
	95% CI (%)	73-98	74-100	65-94	77-100	74-99	80-100	88-100	80-100	14-37
	N	30	12	30	14	25	17	28	17	61
Serogroup C										
1	n (%) ≥ 1:8	1 (3)	2 (17)	2 (7)	3 (21)	2 (8)	4 (24)	3 (11)	8 (47)	0 (0)
	95% CI (%)	0.084-17	2-48	1-22	5-51	1-26	7-50	2-28	23-72	0-6
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:8	30 (100)	12 (100)	30 (100)	14 (100)	23 (92)	17 (100)	28 (100)	17 (100)	7 (11)
	95% CI (%)	88-100	74-100	88-100	77-100	74-99	80-100	88-100	80-100	5-22
	N	30	12	30	14	25	17	28	17	61
Serogroup W										
1	n (%) ≥ 1:8	9 (31)	4 (3)	4 (13)	6 (43)	10 (40)	5 (29)	6 (21)	9 (53)	1 (2)
	95% CI (%)	15-51	10-65	4-31	18-71	21-61	10-56	8-41	28-77	0.041-9
	N	29	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:8	27 (93)	12 (100)	30 (100)	14 (100)	24 (96)	16 (94)	28 (100)	16 (94)	6 (10)
	95% CI (%)	77-99	74-100	88-100	77-100	80-100	71-100	88-100	71-100	4-20
	N	29	12	30	14	25	17	28	17	61
Serogroup Y										
1	n (%) ≥ 1:8	11 (37)	5 (42)	10 (33)	10 (71)	8 (32)	8 (47)	9 (32)	10 (59)	1 (2)
	95% CI (%)	20-56	15-72	17-53	42-92	15-54	23-72	16-52	33-82	0.041-9
	N	30	12	30	14	25	17	28	17	61
44	n (%) ≥ 1:8	29 (97)	11 (92)	30 (100)	14 (100)	24 (96)	17 (100)	28 (100)	16 (94)	23 (38)
	95% CI (%)	83-100	62-100	88-100	77-100	80-100	80-100	88-100	71-100	26-51
	N	30	12	30	14	25	17	28	17	61

Source: [Table 11.4.1.2-2] Table 14.2.1.6. Individual subject results: Appendix 16.2.6.1.

Table 2.0-5 Geometric Mean hSBA Titers After Challenge With One Dose of Licensed PS Vaccine

Day	hSBA	ACWY10		A10CWY5		ACWY5		ACWY2.5		Naive
		1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	1 dose	2 doses	
Serogroup A										
1	GMT	2	2	2.25	3.38	2.11	2.6	2.13	2.62	2
	95% CI	1.74-2.3	1.6-2.49	1.95-2.58	2.76-4.15	1.81-2.46	2.16-3.13	1.84-2.46	2.18-3.16	1.81-2.21
	N	30	12	30	14	25	17	28	17	61
44	GMT	57	145	78	208	96	83	91	171	3.98
	95% CI	34-95	65-325	47-130	99-439	55-168	42-163	54-154	87-337	2.79-5.7
	N	30	12	30	14	25	17	28	17	61
Day 44/ Day 1	GMR	28	73	35	62	46	32	43	65	1.99
	95% CI	17-47	33-158	21-57	30-126	27-78	17-61	26-71	34-125	1.41-2.81
	N	30	12	30	14	25	17	28	17	61
Serogroup C										
1	GMT	2.36	3.73	2.52	4.02	2.46	4.16	2.44	6.03	2.04
	95% CI	1.8-3.1	2.42-5.74	1.92-3.31	2.7-6	1.83-3.32	2.89-5.97	1.84-3.24	4.2-8.67	1.68-2.47
	N	30	12	30	14	25	17	28	17	61
44	GMT	500	505	610	716	574	419	521	818	2.9
	95% CI	322-778	251-1015	392-949	375-1366	354-932	233-754	330-823	455-1470	2.13-3.96
	N	30	12	30	14	25	17	28	17	61
Day 44/ Day 1	GMR	212	136	242	178	233	101	213	136	1.43
	95% CI	133-339	64-285	151-387	90-354	139-390	54-188	131-347	73-253	1.03-1.98
	N	30	12	30	14	25	17	28	17	61
Serogroup W										
1	GMT	4.5	4.22	3.22	7.91	6.88	4.42	4.65	11	2.06
	95% CI	3.05-6.66	2.29-7.75	2.19-4.73	4.5-14	4.51-10	2.65-7.37	3.12-6.92	6.82-19	1.57-2.7
	N	29	12	30	14	25	17	28	17	61
44	GMT	283	680	569	738	750	409	400	1087	2.79
	95% CI	158-507	274-1685	320-1010	318-1711	400-1407	190-876	221-724	507-2332	1.86-4.17
	N	29	12	30	14	25	17	28	17	61
Day 44/ Day 1	GMR	63	161	177	93	109	92	86	96	1.35
	95% CI	36-108	69-375	103-301	43-204	61-196	45-188	49-150	47-194	0.93-1.97
	N	29	12	30	14	25	17	28	17	61
Serogroup Y										
1	GMT	4.88	7.5	4.81	10	5.27	7.31	5.84	13	2.05
	95% CI	3.28-7.24	4.01-14	3.24-7.14	5.65-18	3.42-8.13	4.32-12	3.88-8.79	7.91-23	1.56-2.71
	N	30	12	30	14	25	17	28	17	61
44	GMT	249	299	587	599	528	350	552	1050	6.62
	95% CI	139-446	119-749	328-1049	256-1403	279-998	162-757	302-1007	485-2273	4.4-9.95
	N	30	12	30	14	25	17	28	17	61
Day 44/ Day 1	GMR	51	40	122	59	100	48	95	79	3.22
	95% CI	31-85	18-89	73-203	28-125	57-175	24-94	56-160	40-154	2.26-4.6
	N	30	12	30	14	25	17	28	17	61

Source: [Table 11.4.1.2-3] Table 14.2.1.10. Individual subject results: Appendix 16.2.6.1.

2 SYNOPSIS

Name of Sponsor Chiron S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Title of study:
A Phase 1, Observer Blind, Randomized, Single Center, Controlled Study to Evaluate the Safety and the Immunogenicity of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with Aluminum Phosphate Adjuvant; or Chiron Meningococcal ACWY Conjugate Vaccine without Adjuvant; or Polysaccharide Meningococcal ACWY Vaccine (GSK Mencevax), in Healthy Adult Subjects

Protocol number: V59P3

Investigator: Silvio Crestani, MD

Study center: Institute for Pharmacokinetic and Analytical Studies, Via Mastri 36, CH - 6853 Ligornetto, Switzerland

Publication (reference): None

Study period: 10 JUL 03 – 11 AUG 03	**Phase of development:** Phase 1

Objectives:
Safety
To evaluate the safety and tolerability of a single dose of the Chiron meningococcal ACWY conjugate vaccine (with aluminum phosphate [adjuvant]), Chiron meningococcal ACWY conjugate vaccine (without aluminum phosphate) and GSK Mencevax vaccine.

Immunogenicity
To evaluate the serum antibody responses 28 days after administration of a single dose of the Chiron meningococcal ACWY conjugate vaccine (with aluminum phosphate [adjuvant]), Chiron meningococcal ACWY conjugate vaccine (without aluminum phosphate) and GSK Mencevax vaccine.

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Methodology:

Approximately 90 healthy adults were to be enrolled and randomized in a 1:1:1 ratio to receive a single intramuscular (IM) injection of either Chiron meningococcal ACWY conjugate vaccine (with aluminum phosphate [adjuvant]) or the same vaccine administered without adjuvant, or GSK Mencevax (i.e., a planned enrolment of 30 in each vaccination group).

Subjects were screened to ensure they were in good health and met all inclusion criteria and no exclusion criteria. Medical history was obtained and a physical examination performed. Blood and urine samples were obtained prior to inclusion into the study for standard clinical laboratory tests. At visit 1 an additional blood sample was taken before the vaccination for testing of baseline antibody levels against meningococcal serogroups A, C, W_{135}, and Y. Study vaccines were administered IM in the deltoid muscle.

Subjects remained in the clinic for 60 minutes after study vaccination. At the end of the 60 minutes, subjects were evaluated for any immediate local and systemic reactions, and other adverse events (AEs). The subjects were then instructed to complete diary cards to describe local reactions (i.e., erythema, induration, swelling and pain), systemic reactions (i.e., malaise, chills, headache, nausea, myalgia and arthralgia), other indicators of reactogenicity (i.e., to record axillary temperature measurements, staying at home due to a reaction, and taking analgesics/antipyretics), and other AEs, daily for 7 days following vaccination (day 1 to 7). A telephone call checked for adverse reactions on the 3rd and 7th day after vaccination. Blood and urine samples were taken 28 days (day 29) after vaccination and diary cards were then collected.

All AEs were collected throughout the duration of the study. If an AE remained unresolved at the conclusion of the study, a clinical assessment was made by the investigator and medical monitor to determine whether continued follow-up of the AE was warranted.

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Number of subjects (planned and analyzed):
Approximately 90 healthy adult subjects between 18 and 45 years of age were planned to be enrolled in this study and randomly assigned, in a 1:1:1 ratio, into three vaccination groups. All vaccinated subjects were to be included in the safety analyses. Subjects who provided evaluable blood samples within the protocol-specified time interval were to be included in immunogenicity analyses.

Actual enrolment, both overall and into each vaccination group was as planned (i.e., 30 subjects were enrolled into each vaccination group). All subjects were vaccinated and therefore included in at least one safety analysis. Three subjects were excluded from both the per-protocol (PP) and intention-to-treat (ITT) populations (one subject was excluded from the immunogenicity analyses of the ACWY adjuvanted vaccine group and the remaining two subjects were excluded from the immunogenicity analysis of the GSK Mencevax group [control]: all three subjects had received a concomitant medication that may have invalidated the postvaccination immunogenicity data).

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria

1) 18 to 45 years of age
2) Mentally competent
3) Able to give written informed consent prior to study entry
4) Available for all the visits scheduled in the study
5) Females with a negative pregnancy test prior to vaccination, and willing to practice adequate contraception for the duration of the trial
6) In good health as determined by:
   - Medical history
   - Screening laboratory tests
   - Physical examination
   - Clinical judgment of the investigator

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Exclusion criteria

Individuals were not to be enrolled into the study if:

1) They were unwilling or unable to give written informed consent to participate in the study
2) They had any serious disease such as:
   a. Cancer
   b. Autoimmune disease
   c. Arteriosclerotic disease or diabetes mellitus
   d. Chronic obstructive pulmonary disease
   e. Acute or progressive hepatic disease
   f. Acute or progressive renal disease
   g. Congestive heart failure
3) They had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component
4) They had a known or suspected impairment/alteration of immune function resulting from:
   a. Receipt of immunosuppressive therapy
   b. Receipt of immunostimulants
   c. Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the 3 months prior to planned enrolment and for the full length of the study
   d. Suspected or known HIV infection or HIV related disease
5) They had had laboratory confirmed N. meningitidis infection
6) They had been immunized with any meningococcal vaccine
7) They had received another vaccine or any investigational agent within 90 days prior to planned enrolment
8) They had experienced any acute respiratory disease or infections requiring systemic antibiotic or antiviral therapy or they had experienced fever ≥ 38°C within 3 days prior to planned enrolment

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9) They were females with positive pregnancy test and/or females who were breastfeeding
10) They had received systemic antibiotic treatment or antiviral therapy within the 7 days prior to planned enrolment
11) They had any condition that, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

Test product, dose, mode of administration, lot number:

A) The investigational Chiron meningococcal ACWY conjugate vaccine (ACWY non-adjuvanted vaccine) was obtained by extemporaneous mixing just before injection of two vials:

Lyophilized Meningococcal A component (Vial A: Chiron Men A Lot No. 005011: Expiry date December 03):

- Men A-CRM_{197} conjugate (b) (4) µg
- (b) (4) (b) (4)
- Potassium dihydrogen phosphate (b) (4)
(adj. to pH (b) (4)

To be diluted with Men CWY full liquid vaccine (Vial B: Chiron Men CWY without adjuvant Lot No. T79P22D1: Expiry date December 03):

- Men C-CRM_{197} conjugate (b) (4) µg
- Men W-CRM_{197} conjugate (b) (4) µg
- Men Y-CRM_{197} conjugate (b) (4) µg
- Sodium chloride (b) (4)
- (b) (4)
- Sodium phosphate monobasic

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

After reconstitution the Men ACWY vaccine had the following composition per 0.5 mL of injectable solution:

- Men A-CRM_{197} conjugate	10 µg
- Men C-CRM_{197} conjugate	10 µg
- Men W-CRM_{197} conjugate	10 µg
- Men Y-CRM_{197} conjugate	10 µg
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic (pH (b) (4)	
- Potassium dihydrogen phosphate	
- (b) (4)	

One 0.5 mL dose of Chiron meningococcal ACWY conjugate non-adjuvanted vaccine was injected IM in the deltoid muscle.

B) The investigational Chiron meningococcal ACWY conjugate vaccine with aluminum phosphate (ACWY adjuvanted vaccine) was obtained by extemporaneous mixing just before injection of two vials:

Lyophilized meningococcal A component (Chiron Men A Lot No. 005011: Expiry date December 03):

- Men A-CRM_{197} conjugate	(b) (4) µg
- (b) (4)	(b) (4)
- Potassium dihydrogen phosphate	
(adj. to pH (b) (4))	

Name of Sponsor Chiron S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

To be diluted with Men CWY full liquid vaccine (Chiron Men CWY with adjuvant Lot No. T79P19D1: Expiry date January 04):

- Men C-CRM_{197} conjugate	(b) (4) µg
- Men W-CRM_{197} conjugate	(b) (4) µg
- Men Y-CRM_{197} conjugate	(b) (4) µg
- Aluminum phosphate	(b) (4) mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic	

After reconstitution ACWY adjuvanted vaccine had the following composition per 0.5 mL of injectable solution:

-Men A-CRM_{197} conjugate	10 µg
-Men C-CRM_{197} conjugate	10 µg
-Men W-CRM_{197} conjugate	10 µg
-Men Y-CRM_{197} conjugate	10 µg
- Aluminum phosphate	0.3 mg Al^{3+}
- Sodium chloride	(b) (4)
- (b) (4)	
- Sodium phosphate monobasic (pH (b) (4))	
- Potassium dihydrogen phosphate	
- (b) (4)	

One 0.5 mL dose of ACWY adjuvanted vaccine was injected IM in the deltoid region.

Duration of study: From 10 JUL 03 to 11 AUG 03

Reference therapy, dose, mode of administration, lot number:

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GSK Mencevax meningococcal ACWY polysaccharide vaccine (control: GSK Mencevax ACWY Lot No. N402A47A: Expiry date October 04)
Each dose of 0.5 mL of vaccine was obtained by extemporaneous mixing just before injection of two vials:

Vial of lyophilized purified polysaccharide of *N. meningitidis* 200 µg (Vial A), of which:

Serogroup A	50 µg
Serogroup C	50 µg
Serogroup W	50 µg
Serogroup Y	50 µg
Lactose	(b) (4)

Vial of diluent (Vial B):

NaCl	4.5 mg
Water	up to 0.5 mL

One 0.5 mL dose of the control vaccine was injected IM in the deltoid muscle.
Please note: GSK Mencevax is licensed for subcutaneous (SC) administration. However, for purposes of comparison in this study, Mencevax was administered IM in the deltoid muscle.

Criteria for evaluation:

Immunogenicity

The immunogenicity of a single dose of the Chiron Conjugate Meningococcal ACWY vaccine with and without aluminum phosphate and of GSK Mencevax for all four serogroups was to be evaluated in terms of:·

- SBA GMT increase at one month after vaccination when compared with baseline values (day 1);·
- Percentage of subjects with SBA titer ≥1:4 before (day 1) and one month after

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vaccination;·
- Percentage of subjects with SBA titer ≥1:8 before (day 1) and one month after vaccination;·
- ELISA (total IgG) geometric mean concentration (GMC) before (day 1) and at one month after vaccination.

Safety
- Percentages of subjects with local (i.e., erythema, induration, swelling and pain) and systemic reactions (i.e., malaise, chills, headache, nausea, myalgia and arthralgia) occurring on the day of vaccination or within the subsequent 6 days (day 1 to day 7).
- Percentages of subjects staying at home due to a reaction or taking analgesics/ antipyretics
- Axillary temperature measurements, daily for 7 days following vaccination (day 1 to 7)
- All other adverse events collected throughout the duration of the study.

Statistical methods:
Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrolment were calculated overall and by vaccine group. Distributions of subjects by sex and ethnic origin were summarized overall and by vaccine group.

For each vaccination group, ELISA geometric mean concentration (GMC), and the median, minimum, and maximum concentration for prevaccination (day 1) and postvaccination (day 29) and associated 95% confidence intervals (CIs) were calculated by exponentiating (base 10) the least squares means of the logarithmically transformed (base 10) concentrations and their 95% CIs obtained from a one-way Analysis of Variance (ANOVA) with factor for vaccine group.

The number and percentages of subjects experiencing local (i.e., erythema, induration, swelling and pain) and/or systemic reactions (i.e., malaise, chills, headache, nausea,

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myalgia, arthralgia) occurring on the day of vaccination or within the following 6 days were summarized. Each local and systemic reaction was summarised by maximal severity and by vaccine group. Erythema, induration and swelling were categorized as none (<10 mm), 10-25 mm, 26-50 mm and >50 mm. Axillary temperature was categorized as none (<38°C), 38-38.9°C, 39-39.9°C and ≥40°C. All other systemic reactions were categorized as none, mild, moderate, and severe. The percentages of subjects who used analgesic and/or antipyretic medications or stayed at home due to a reaction were summarized by vaccine group. Summaries by time of onset were also provided. Each local and systemic reaction was categorized as none vs. any and the percentages of subjects reporting each reaction were compared between vaccine groups using the chi-square test or Fisher's Exact test if 20% of the cells had an expected cell frequency less than 5 or if any expected cell frequency was less than 1.

AEs were coded using MedDRA, version 5.0 or higher, and summarized in frequency tables according to preferred term and System Organ Class (SOC). When an AE occurred more than once for a particular subject, the maximal severity and worst causality were counted. The percentages of subjects experiencing AEs considered possibly or probably related to the study vaccine were summarized by vaccine group. All serious adverse events (SAEs) and AEs leading to premature withdrawal from the study were listed. Additionally, AEs that were unrelated to vaccine were summarized by vaccine group. Data listings of all AEs are provided.

Summary and Conclusions:

Immunogenicity results

In total 90 subjects were enrolled into the study, 30 in each vaccination group. All subjects received the vaccine assigned by the randomization list. Three subjects prematurely withdrew from the study before the second blood draw (day 29). All three subjects had received a medication that may have impacted the immunogenicity results. Data from all 90 subjects enrolled into the study were included in the analyses for demographic and other baseline characteristics. All demography and other baseline

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characteristics were similarly distributed among the vaccination groups.

Evaluation of the immunogenicity criteria was by total IgG ELISA only. At baseline the GMCs were similar among the vaccination groups when compared by serogroup (vaccine group ranges were 4.78 – 5.7 µg/mL, 0.4 – 1.07 µg/mL, 0.58 – 1.15 µg/mL, 0.97 – 1.21 µg/mL for serogroups A, C, W and Y respectively). All GMCs increased after vaccination (day 29/day 1 GMRs vaccine group ranges were 5.35 – 12, 31 – 44, 34 – 46, 47 – 66 for serogroups A, C, W and Y respectively). Subset analyses of the PP population (excluding data from 12 subjects who had been previously exposed to a meningococcal vaccination from the analysis of at least one serogroup) suggest that previous exposure to meningococcal vaccination did not alter the overall result of the pre-planned analysis.

Considering that the study was primarily designed to assess vaccine tolerability together with the limitation of the total IgG ELISA (that measures high and low avidity antibodies), it can be concluded from the overall immunogenicity profile that both vaccines formulated with and without adjuvant induced a satisfactory immune response.

Safety results

In total 90 subjects were enrolled into this study. All subjects were exposed to the vaccines assigned by the randomization list.

The percentages of subjects in the ACWY adjuvanted vaccine and the control groups experiencing at least one local reaction (i.e., erythema, induration, swelling, pain) were similar (40% and 43%, respectively) but higher than that of the ACWY non-adjuvanted vaccine group (10%). Pain was the most frequently experienced local reaction (33% of the ACWY adjuvanted vaccine group, 7% of the ACWY non-adjuvanted vaccine group, and 40% of the control group). Most local reactions were mild or moderate in severity (only 2/90 subjects reported a severe local reaction), most (22 subjects reported onset of local reactions on the day of vaccination versus 6 subjects reporting onset thereafter)

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occurred on the day of vaccination, and all resolved within the 7-day observation window.

Systemic reactions (i.e., malaise, chills, headache, nausea, myalgia, arthralgia) were experienced by 20% of ACWY adjuvanted vaccine recipients and ACWY non-adjuvanted vaccine recipients, and 13% of the control. All systemic reactions were reported as mild or moderate in severity and mostly onset within 48 hr of injection: all but one resolved within the 7-day observation window. The most common systemic reaction was headache (experienced by 13%, 17%, 10% of recipients of ACWY adjuvanted vaccine, ACWY non-adjuvanted vaccine, and control vaccine, respectively).

Only one subject (3% of the control group) was recorded with a body temperature ≥ 38°C, two subjects stayed at home (one [3%] in the ACWY non-adjuvanted vaccine group and one [3%] in the control group) and 6 subjects (all [20%] in the ACWY non-adjuvanted vaccine group) received analgesics/antipyretics during the study.

AEs judged to be at least possibly related to the vaccine were only experienced by 3 subjects. All three subjects (10%) were in the ACWY non-adjuvanted vaccine group.

No deaths occurred in this study and no subject experienced an unexpected AE judged to be at least possibly related to vaccination. Two subjects experienced an SAE. Both SAEs (a road traffic accident and a tonsillitis) were judged to be unrelated to the study vaccination. No subject withdrew from the study due to an AE.

The higher percentage of subjects experiencing local reactions in the group that received the investigational vaccine containing adjuvant may not be attributed to the presence of aluminum phosphate adjuvant, as it was similar to that experienced in the group who received the control vaccine in which no adjuvant is present.

Moreover the percentages of subjects experiencing systemic reactions were similar among the three groups, thus demonstrating that both investigational vaccines were as

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safe and as well tolerated as the licensed control vaccine.

Conclusions

In conclusion, administration of MenACWY conjugate vaccine formulation either with or without aluminum phosphate adjuvant was not associated with clinically significant safety concerns and appeared to be well-tolerated in healthy adult volunteers, with reactogenicity profiles similar to a licensed MenACWY polysaccharide vaccine. Both conjugate vaccine formulations were immunogenic and induced IgG anticapsular antibody titers, as measured by total IgG ELISA, that were similar to the control group.

These results support further evaluation of the MenACWY conjugate vaccine formulations either with or without aluminum phosphate adjuvant in younger age groups.

Table 2.1-1 Time and Events

STUDY VISIT DAY	**S**	**1**	**Phone Call**	**Phone Call**	**29**
STUDY DAY NUMBER	**-14 to 1**	**1**	**3[a]**	**7[a]**	**29 to 36**
Obtain Informed Consent	X				
Medical History	X	X			
Complete Physical Examination	X	X			X
Screen for Admission Criteria	X	X			
Follow-up Telephone Call			X	X	
Blood Draw for Assays	X	X			X
Urine sample for Assays	X				X
Measure Axillary Temperature		X			
Immunization		X			
Injection-site Examination		X			X
Assess Local/Systemic Reactions		X	X	X	X
Assess Concomitant Medications	X	X	X	X	X
Assess Adverse Events		X	X	X	X
Diary Card Review[b]					X
Complete Study Termination					X

[a] The telephone calls should have been completed as close to days 3 and 7 as possible.

[b] Collect diary card and reconcile with the data on the "Local and Systemic Reaction" CRF, collected at the day 3 and 7 phone calls.

SUMMARY RESULT TABLES

Table A: Total IgG ELISA GMCs and GMRs

Serogroup	Vaccine group	GMCs μg/mL (95% CIs)		
		day 1	day 29	day 29/day 1
A	ACWY + adjuvant	4.78 (3.1-7.38)	26 (16-42)	5.35 (3.32-8.63)
	ACWY without adjuvant	5.61 (3.67-8.6)	42 (26-68)	7.48 (4.68-12)
	Control	5.7 (3.67-8.87)	69 (42-114)	12 (7.43-20)
C	ACWY + adjuvant	0.4 (0.21-0.76)	16 (10-26)	40 (21-76)
	ACWY without adjuvant	0.74 (0.4-1.39)	23 (15-37)	31 (17-59)
	Control	1.07 (0.56-2.05)	48 (30-76)	44 (23-85)
W	ACWY+ adjuvant	0.58 (0.37-0.92)	27 (15-47)	46 (26-80)
	ACWY without adjuvant	1.15 (0.73-1.8)	39 (22-68)	34 (20-59)
	Control	0.9 (0.57-1.44)	35 (20-62)	39 (22-69)
Y	ACWY + adjuvant	0.98 (0.59-1.62)	61 (37-101)	62 (35-111)
	ACWY without adjuvant	0.97 (0.59-1.59)	64 (39-105)	66 (38-117)
	Control	1.21 (0.73-2.02)	56 (34-94)	47 (26-83)

Table B: Reactogenicity Summary

Numbers (and percentages) of subjects reporting at least one selected local reaction, systemic reaction or other indicator or reactogenicity within 7 days of immunization			
	ACWY adjuvanted vaccine N = 30	**ACWY non-adjuvanted vaccine N = 30**	**Control Vaccine N = 30**
With any postinjection reaction	14 (47%)	8 (27%)	16 (53%)
With local reactions	12 (40%)	3 (10%)	13 (43%)
With systemic reactions	6 (20%)	6 (20%)	4 (13%)
With other[a] postinjection reactions	0	6 (20%)	1 (3%)

[a] "other" postinjection reactions are oral temperature ≥38°C, stayed home due to reaction, use of analgesics or antipyretics

Table C: Summary of Other AEs

AEs other than selected local and systemic reactions reported within 30 days of immunization			
	ACWY adjuvanted vaccine (N=30)	**ACWY non-adjuvanted vaccine (N=30)**	**Control Vaccine (N=30)**
With AE	1 (3%)	5 (17%)	2 (7%)
With at least possibly related AE	0	3 (10%)	0
With serious AE	1 (3%)	0	1 (3%)
With at least possibly related serious AE	0	0	0

Table D: Local Reactogenicity Reported Within 7 days of Immunization

Numbers (and percentages) of subjects reporting each local reaction within 7 days of immunization						
	ACWY adjuvanted vaccine N = 30		**ACWY non-adjuvanted vaccine N = 30**		**Control Vaccine N = 30**	
Local reactions	All	Severe	All	Severe	All	Severe
Erythema [a]	2 (7%)	1 (3%)	1 (3%)	1 (3%)	0	0
Induration [a]	0	0	0	0	1 (3%)	0
Swelling [a]	0	0	0	0	0	0
Pain	10 (33%)	0	2 (7%)	0	12 (40%)	0

[a] severe is defined as >50mm

Table E Systemic Reactogenicity

Numbers (and percentages) of subjects reporting each systemic reaction within 7 days of immunization							
		ACWY adjuvanted vaccine		ACWY non-adjuvanted vaccine		Control Vaccine	
		N = 30		N = 30		N = 30	
		All	Severe	All	Severe	All	Severe
Systemic reactions	Malaise	1 (3%)	0	0	0	0	0
	Chills	1 (3%)	0	1 (3%)	0	0	0
	Headache	4 (13%)	0	5 (17%)	0	3 (10%)	0
	Nausea	2 (7%)	0	1 (3%)	0	0	0
	Myalgia	1 (3%)	0	0	0	1 (3%)	0
	Arthralgia	0	0	1 (3%)	0	0	0
Others	Axillary Temperature ≥ 38 °C	0	NA	0	NA	1 (3%)	NA
	Stayed Home Due to Reaction	0	NA	1 (3%)	NA	1 (3%)	NA
	Analgesic/Antipyretic Medication Used	0	NA	6 (20%)	NA	0	NA

2.0 SYNOPSIS

Name of Sponsor Chiron Vaccines 4560 Horton Street Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Chiron Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P4**	

Title of study: A Phase 2, Randomized, Double-Blind, Multicenter Trial to Evaluate the Safety and Immune Response of Different Formulations of Chiron Conjugate Meningococcal ACWY Vaccine With or Without Aluminum Phosphate Adjuvant Administered to Healthy Toddlers 12 to 16 Months of Age and to Assess the Safety and Immunogenicity of a Single Dose of Licensed Meningococcal Polysaccharide Vaccine, Menomune®, When Administered to Children 3 to 5 Years of Age (Open Label)

Protocol number: V59P4

Investigators: William Kennedy, MD; Keith Reisinger, MD; Milo D. Hilty, MD; Steven Black, MD; Katherine Vaughn, MD; Tracy Bridges, MD.

Study centers: UCLA Center for Vaccine Research, Torrance, Calif; Primary Physicians Research, Inc., Pittsburgh, Pa; Pediatric Clinical Trials International, Inc., Columbus, Ohio; Kaiser Permanente Vaccine Study Center, Oakland, Calif; The Vancouver Clinic, Inc., PS, Vancouver, Wash; Georgia Pollens Clinical Research Centers, Inc., Albany, Ga.

Publication (reference): None

Study period: 03 NOV 03 to 11 OCT 04	**Phase of development:** Phase 2

Objectives:

Safety Objective:

To assess the safety and tolerability of a single dose of three formulations of Chiron's Meningococcal ACWY Conjugate Vaccine (one formulation with aluminum phosphate adjuvant contains 5 µg of each oligosaccharide antigen, and two formulations without aluminum phosphate adjuvant contain either 5 µg or 10 µg of each oligosaccharide antigen).

Menomune® is a registered trademark of Sanofi Pasteur Inc. (formerly Aventis Pasteur).

Immunogenicity Objectives:

Primary

To assess the immunogenicity of a single dose of Chiron Meningococcal ACWY Conjugate Vaccine containing 5 µg of each oligosaccharide and formulated with aluminum phosphate adjuvant, in comparison with the same formulation without aluminum phosphate adjuvant (percentage of subjects with serum bactericidal activity using human complement [hC'SBA] of 1:4 or greater against *N meningitidis* serogroups A, C, W-135, and Y).

Secondary

- To assess the immunogenicity of a single dose of Chiron Meningococcal ACWY Conjugate Vaccine containing 5 µg of each oligosaccharide and formulated with aluminum phosphate adjuvant, in comparison with the same formulation without aluminum phosphate adjuvant (hC'SBA geometric mean titer [GMT] antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y).
- To assess the immunogenicity of a single dose of Chiron Meningococcal ACWY Conjugate Vaccine containing 5 µg of each oligosaccharide and formulated with aluminum phosphate adjuvant, in comparison with the Chiron Meningococcal ACWY Conjugate Vaccine containing 10 µg of each oligosaccharide and formulated without aluminum phosphate adjuvant (hC'SBA GMT antibody response and percent response hC'SBA of 1:4 or greater directed against *N meningitidis* serogroups A, C, W-135, and Y).
- To assess the immunogenicity (hC'SBA GMT and hC'SBA percent response of 1:4 or greater) of the Chiron Meningococcal ACWY Conjugate Vaccine formulated without aluminum phosphate adjuvant when administered as either 5 or 10 µg per oligosaccharide.
- To assess immunogenicity (hC'SBA GMT and hC'SBA percent response of 1:4 or greater) of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune) when administered to children 3 to 5 years of age (group IV).

Persistence of Immune Response (Amendment 5 Only; Results in Amendment 5 Addendum Report)

To evaluate the persistence of antibodies to *N meningitidis* serogroups A, C, W135, and Y (expressed as GMT and as percentage of subjects with SBA ≥ 1:4 directed against *N meningitidis* serogroups A, C, W-135, and Y) in children approximately 12 months following immunization with either one dose of Chiron MenACWY conjugate vaccine (formulations with and without aluminum phosphate, Groups I, II, and III) or one dose of a licensed meningococcal polysaccharide vaccine, Menomune (Group IV).

Methodology: This was a phase 2, randomized, double-blind, multicenter trial. Healthy toddlers were enrolled and randomized in a 1:1:1 ratio to one of three vaccination groups (groups I, II, and III). Toddler subjects in groups I to III received a single dose of one of three formulations of Chiron Meningococcal ACWY Conjugate Vaccine administered intramuscularly (IM) in the left deltoid. The protocol was

amended to include an additional study group (non-randomized, open-label group IV) of healthy children 3 to 5 years old who received a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune) administered subcutaneously (SC) in the left upper arm. Study groups and meningococcal vaccines are summarized in the following table.

Groups I-III: MenACWY Conjugate Vaccine Oligosaccharide Content (µg/serogroup)					
Group	**MenA**	**MenC**	**MenW-135**	**MenY**	**Adjuvant**
I	10	10	10	10	(-)
II	5	5	5	5	(-)
III	5	5	5	5	(+)
Group IV: MenACWY Polysaccharide Vaccine Polysaccharide Content (µg/serogroup)					
IV	50	50	50	50	(-)

After the vaccination of toddlers in groups I to III, a telephone call with the parent/guardian was made to check each subject's status on day 3 and day 8 (groups I to III only). All subjects returned to the clinic on day 29 to provide blood samples for immunogenicity assays and to be evaluated for reactogenicity and adverse events (AE). For all groups, a follow-up telephone call was made at day 180 (i.e., 6 months) following study immunization to assess the occurrence of significant medical events, such as hospitalizations and emergency room visits, during the follow-up period.

Number of subjects (planned and analyzed): 300 subjects planned, including 225 subjects in groups I, II, and III and 75 subjects in group IV. 316 subjects analyzed, including 236 subjects in groups I, II, and III and 80 subjects in group IV.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria (Toddlers, Groups I to III)

Individuals eligible for enrollment in this study were male and female healthy toddlers who were:

1. 12 to less than 17 months of age whose parents or legal guardians gave written informed consent before study vaccination;
2. available for all visits and telephone calls scheduled for the study;
3. in good health as determined by:
   - medical history;
   - physical examination;
   - clinical judgment of the investigator;
4. up to date with age-appropriate immunizations for diphtheria, tetanus, pertussis,

polio, hepatitis B, *Haemophilus influenzae* type b, and pneumococcus to include the following antigens:

- Diphtheria, Tetanus, acellular Pertussis (DTaP 3 doses);
- Inactivated Polio Virus (IPV, 2 or 3 doses);
- Hepatitis B (HB);
- *H influenzae* type b (Hib, at least 2 doses if PRP-OMPC or 3 doses of other licensed Hib vaccine);
- Pneumococcal conjugate vaccine (at least 3 doses).

Exclusion Criteria (Toddlers, Groups I to III)

Individuals were not to be enrolled in the study if:

1. their parents or legal guardians were unwilling or unable to give written informed consent to participate in the study;
2. they had previous laboratory confirmation of *N meningitidis* infection or a history of a previous disease believed to be related to any meningococcal infection;
3. they had household contact and/or intimate exposure in the previous 30 days (prior to study vaccination) to an individual with ascertained *N meningitidis*;
4. they had experienced within the previous 7 days significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or had experienced fever (38°C [100.4°F] or higher) within the previous 3 days;
5. they had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (EXCEPTION: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cefalexin, etc.] could have been enrolled 7 days following the last dose);
6. they had any serious chronic disease such as cardiac disease, autoimmune disease, insulin-dependent diabetes, urologic disorders, renal disease, pulmonary disease, etc.;
7. they had a known or suspected impairment /alteration of immune function resulting from (for example):
   - immunosuppressive therapy within the past 30 days (systemic corticosteroid administered for more than 5 days or in a daily dose greater than 1 mg/kg/day prednisone or equivalent for 5 days or less or cancer chemotherapy);
   - immunostimulants;
   - parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within the past 90 days and for the full length of the study;
   - suspected or known HIV infection or HIV-related disease;
8. they had Down's syndrome or other known cytogenic disorders;
9. they had a history of seizures or serious neurological disease;
10. they were known to have had a bleeding diathesis or any condition that may have been associated with a prolonged bleeding time;
11. they had received another vaccine within the previous 30 days or expected to

receive another vaccine during the 28-day study period (EXCEPTION: subjects were excluded if they received an inactive influenza vaccine within 15 days before study immunization or expected to receive an inactive influenza vaccine within 15 days after immunization with study vaccine);

12. they had received a live viral vaccine within the previous 60 days;
13. they had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
14. they had received any investigational agent within the previous 90 days or expected to receive any investigational agent during the 28-day study period;
15. their families planned to leave the area of the study site before the end of the study period;
16. they had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Inclusion Criteria (Preschoolers, Group IV)

Individuals eligible for enrollment into this study were male and female healthy children who were:

1. 3 to less than 6 years of age whose parents or legal guardians gave written informed consent before study vaccination;
2. available for all visits and telephone calls scheduled for the study;
3. in good health as determined by:
   - medical history;
   - physical examination;
   - clinical judgment of the investigator;
4. up to date with age-appropriate immunizations.

Exclusion Criteria (Preschoolers, Group IV)

Individuals were not to be enrolled in the study if:

1. their parents or legal guardians were unwilling or unable to give written informed consent to participate in the study;
2. they had previous laboratory confirmation of *N meningitidis* infection or a history of a previous disease believed to be related to any meningococcal infection;
3. they had previous household contact and/or intimate exposure in the previous 30 days (before study vaccination) to an individual with ascertained *N meningitidis*;
4. they had experienced within the previous 7 days significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or had experienced fever (38°C [100.4°F] or higher) within the previous 3 days;
5. they had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (EXCEPTION: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cefalexin, etc.] could have been enrolled 7 days following the last dose);
6. they had any serious chronic disease such as cardiac disease, autoimmune disease,

insulin-dependent diabetes, urologic disorders, renal disease, pulmonary disease, etc.;

7. they had a known or suspected impairment /alteration of immune function resulting from (for example):
   - immunosuppressive therapy within the past 30 days (systemic corticosteroid administered for more than 5 days or in a daily dose greater than 1 mg/kg/day prednisone or equivalent for 5 days or less or cancer chemotherapy);
   - immunostimulants;
   - parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within the past 90 days and for the full length of the study;
   - suspected or known HIV infection or HIV related disease;
8. they had Down's syndrome or other known cytogenic disorders;
9. they had a history of seizures or serious neurological disease;
10. they were known to have a bleeding diathesis, or any condition that may have been associated with a prolonged bleeding time;
11. they had received another vaccine within the previous 30 days or expected to receive another vaccine during the 28-day study period (EXCEPTION: subjects were excluded if they received an inactive influenza vaccine within 15 days before study immunization or expected to receive an inactive influenza vaccine within 15 days after immunization with study vaccine);
12. they had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
13. they had received any investigational agent within the previous 90 days or expected to receive any investigational agent during the 28-day study period;
14. their families planned to leave the area of the study site before the end of the study period;
15. they had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Test product, dose, mode of administration, lot number:

Single dose injection, IM (left deltoid)

Groups I, II, and III received different formulations of the investigational Chiron MenACWY Conjugate Vaccine obtained by extemporaneous mixing immediately before injection of the lyophilized MenA component (5 µg lot 010011; 10 µg lot 009011) to be resuspended with the MenCWY full liquid vaccine (5 µg with adjuvant lot T79P20D1; 5 µg without adjuvant lot T79P23D1; 10 µg without adjuvant lot T79P22D1). Batch lot numbers for each two-vial package product were:

- (b) (4) : 10 µg MenA + 10 µg MenCWY without adjuvant = T79P22D1;
- (b) (4) : 5 µg MenA + 5 µg MenCWY without adjuvant = T79P23D1;
- (b) (4) : 5 µg MenA + 5 µg MenCWY with adjuvant = T79P20D1.

Group I: Chiron MenACWY Conjugate Vaccine (**non-adjuvanted, 10 µg**) had the following composition per 0.5 mL of injectable suspension:

MenA CRM_{197} conjugate	10 µg MenA oligosaccaride; (b) (4) µg CRM_{197}
MenC CRM_{197} conjugate	10 µg MenC oligosaccharide; (b) (4) µg CRM_{197}
MenW CRM_{197} conjugate	10 µg MenW-135 oligosaccharide; (b) (4) µg CRM_{197}
MenY CRM_{197} conjugate	10 µg MenY oligosaccharide; (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

CRM = cross-reactive material

Group II: Chiron MenACWY Conjugate Vaccine (**non-adjuvanted, 5 µg**) had the following composition per 0.5 mL of injectable suspension:

MenA CRM_{197} conjugate	5 µg MenA oligosaccharide; (b) (4) µg CRM_{197}
MenC CRM_{197} conjugate	5 µg MenC oligosaccharide; (b) (4) µg CRM_{197}
MenW CRM_{197} conjugate	5 µg MenW-135 oligosaccharide; (b) (4) µg CRM_{197}
MenY CRM_{197} conjugate	5 µg MenY oligosaccharide; (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

Group III: Chiron MenACWY Conjugate Vaccine (**adjuvanted, 5 µg**) had the following composition per 0.5 mL of injectable suspension:

MenA CRM_{197} conjugate	5 µg MenA oligosaccaride; (b) (4) µg CRM_{197}
MenC CRM_{197} conjugate	5 µg MenC oligosaccaride; (b) (4) µg CRM_{197}
MenW CRM_{197} conjugate	5 µg MenW-135 oligosaccharide; (b) (4) µg CRM_{197}
MenY CRM_{197} conjugate	5 µg MenY oligosaccharide; (b) (4) µg CRM_{197}
Aluminum phosphate	0.3 mg Al^{3+}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

Duration of study: Each subject participated for 6 months in the Amendment 4 study. Subjects enrolled in Amendment 5 participated for an additional 6 months for a total of 1 year. Each subject received a single injection of study vaccine on day 1, returned to the clinic on day 29 for post-vaccination assessments, and provided an interim adverse

event history when contacted by research staff at 6 months after vaccination.

Reference therapy, dose, mode of administration, lot number: Menomune

Single dose injection, SC (left upper arm)

Group IV received Menomune. Menomune is licensed in the United States and is manufactured by Sanofi Pasteur Inc. (formerly Aventis Pasteur) (Swiftwater, Pa). Menomune (lot number UB349AB) was supplied in single dose vials (1 dose/vial) and is reconstituted with 0.6 mL of diluent. The vaccine consists of four meningococcal capsular polysaccharide serogroups (A, C, Y, and W-135). The indicated dose is 50 µg of each of the polysaccharides.

Composition	Quantity
Isolated product from each of groups A, C, Y, and W-135	50 µg
Lactose	2.5 to 5 mg
Liquid diluent	
Sterile water for injection	(b) (4) mL

0.5 mL of reconstituted Menomune is administered subcutaneously.

Criteria for evaluation:

Immunogenicity

Serum bactericidal activity was measured for each serogroup and expressed as GMT and percent of subjects with hC'SBA response of 1:4 or greater and 1:8 or greater. Additional enzyme-linked immunosorbent assays (ELISA) were performed to further characterize the immune response.

Safety

Groups I, II, and III: Measures of safety and reactogenicity included data from observed local reactions (e.g., tenderness, erythema, and induration) and systemic reactions (e.g., change in eating habits, sleepiness, persistent crying lasting more than 3 hours, irritability, vomiting, and diarrhea). These data were collected together with axillary temperature, analgesic or antipyretic medication use, and all other adverse events during the first 7 days after the injection, including the day of vaccination (study days 1 through 7). Serious adverse events (SAE) and/or adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

Group IV was added to provide immunogenicity data from sera taken from 3- to 5-year-old subjects who received a dose of a licensed meningococcal polysaccharide vaccine, Menomune. Serious adverse events and/or adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

Statistical methods:

Immunogenicity

The primary immunogenicity objective was to compare the percent of responders (defined as the percentage of subjects with hC'SBA titers ≥ 1:4) in group II vs. group III

against each of the four components. Other comparisons of interest included comparing percent of responders in group I vs. group II and group I vs. group III. These comparisons were also made on log-transformed hC'SBA GMTs.

Safety

All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 7.1, and grouped by MedDRA preferred terms into frequency tables according to MedDRA system-organ-class categories. Local and systemic reactions (groups I to III only) were evaluated by the chi-square or Fisher's exact test as appropriate for expected cell counts.

Preliminary Analysis

To facilitate the planning of future trials, an unblinded preliminary immunogenicity and 1-month safety analysis (including local and systemic post-immunization reactions within 7 days after immunization) was performed after all subjects had completed visit 2 (approximately 1 month [range 28 to 34 days] after immunization, hereinafter referred to as "day 29"). As stated in the protocol, the results of the preliminary analysis were not intended to, and did not, alter the course of the trial.

Summary and Conclusions:

Three hundred sixteen (316) subjects were enrolled into the study through amendment 4 of the protocol. This clinical study report (CSR) is based on the first four amendments. An addendum CSR will be prepared for the fifth amendment of the protocol (no additional subjects were enrolled under the fifth protocol amendment).

Among the 316 enrolled subjects, 236 toddlers between 12 and 16 months of age were enrolled and randomized to Chiron's Conjugate Meningococcal Vaccine groups, including 82 subjects randomized to the 10 μg non-adjuvanted MenACWY vaccination group (10ACWY–), 79 subjects randomized to the 5 μg non-adjuvanted group (5ACWY–), and 75 subjects randomized to the 5 μg adjuvanted group (5ACWY+). Eighty (80) children between 3 and 5 years of age were enrolled and assigned to the open-label Menomune vaccine group.

Three hundred fifteen (315) subjects were vaccinated. The parents or legal guardian of one subject withdrew the subject from participation before vaccination due to unwillingness to allow the subject to undergo blood draws for serology.

Three hundred four (304) subjects completed the protocol, including 98%, 96%, 96%, and 95% of 10ACWY–, 5ACWY–, 5ACWY+, and Menomune subjects, respectively. Among the 12 subjects who did not complete the study, none of the subjects was withdrawn due to local or systemic reactions or due to adverse events. Two subjects withdrew consent, and 10 subjects were lost to follow-up.

Chiron MenACWY subjects were 12 to 16 months of age, and the average age was similar among toddler groups (13.2 months, 12.9 months, and 13.1 months for 10ACWY–, 5ACWY–, and 5ACWY+ groups, respectively). Male:female ratios were similar among toddler groups (54%:46%, 51%:49%, and 52%:48%, respectively). Most of the subjects were Caucasian (62%, 54%, and 59%, respectively), and ethnic origins

of other subjects were similarly distributed among the vaccination groups. Body weights ranged from 7.7 to 14.5 kg, and mean weights were approximately 10 kg in each toddler group.

Menomune subjects were 36 to 70 months of age (mean, 49.1 months), 46%:54% male:female, and 91% Caucasian. Body weights ranged from 13.6 to 34.5 kg (mean, 17.54 kg).

Immunogenicity results

In the primary immunogenicity analysis, both non-adjuvanted and adjuvanted 5 μg MenACWY groups (5ACWY– and 5ACWY+ groups, respectively) exhibited increased serum bactericidal activity (percentage of subjects with hC'SBA titers ≥ 1:4) relative to baseline for each serogroup. No statistically significant difference between the two groups was observed for any of the four serogroups ($P > .05$ in each pairwise test; A, 50% vs. 45%; C, 91% vs. 89%; W, 65% vs. 77%; Y, 85% vs. 81%, respectively).

In secondary analyses, GMT for both 5ACWY– and 5ACWY+ groups increased by 3- to 10-fold above baseline by day 29 (approximately 1 month following immunization). No statistically significant difference between 5ACWY– and 5ACWY+ groups was observed in day 29 GMTs for the four serogroups ($P > .05$ in each pairwise test: A, 5.92 vs. 7.15; C, 20 vs. 20; W, 8.07 vs. 13; Y, 20 vs. 15, respectively). For the W serogroup, the 8.07 vs. 13 comparison was **marginally statistically significant ($P = .054$)** in the 5ACWY– vs. 5ACWY+ comparison.

Additionally, both non-adjuvanted and adjuvanted 5 μg groups (5ACWY– and 5ACWY+ groups, respectively) also exhibited increases from baseline in the percent of subjects with hC'SBA titers ≥ 1:8 for each serogroup. No statistically significant difference between the two groups was observed for serogroup A, C, and Y antigens ($P > .05$; A, 38% vs. 40%; C, 80% vs. 81%; Y, 78% vs. 68%, respectively). However, the difference between 5ACWY– and 5ACWY+ for the **W antigen was statistically significant (53% vs. 71%; $P = .033$)**.

In secondary comparisons between non-adjuvanted 10 μg and adjuvanted 5 μg groups (10ACWY– and 5ACWY+ groups, respectively), both groups exhibited an increased percentage of subjects with hC'SBA titers ≥ 1:4 relative to baseline for each serogroup. No statistically significant difference was observed between the 10ACWY– and 5ACWY+ groups in the percent of subjects with hC'SBA titers ≥ 1:4 for any of the four serogroups ($P > .05$ in each pairwise test; A, 41% vs. 45%; C, 93% vs. 89%; W, 79% vs. 77%; Y, 84% vs. 81%, respectively).

There were also no statistically significant differences in day 29 GMT between 10ACWY– and 5ACWY+ groups for any of the four serogroups ($P > .05$ in each pairwise test; A, 5.84 vs. 7.15; C, 21 vs. 20; W, 13 vs. 13; Y, 21 vs. 15, respectively).

Additionally, there were also no statistically significant differences between 10ACWY– and 5ACWY+ groups in the percent of subjects with hC'SBA titers ≥ 1:8 for any of the four serogroups ($P > .05$; A, 40% vs. 40%; C, 80% vs. 81%; W, 69% vs. 71%; Y, 75%

vs. 68%, respectively).

In secondary comparisons between non-adjuvanted 10 μg and non-adjuvanted 5 μg MenACWY groups (10ACWY– and 5ACWY– groups, respectively), both groups exhibited an increased percentage of subjects with hC'SBA titers ≥ 1:4 relative to baseline for each serogroup. No statistically significant difference was observed between 10ACWY– and 5ACWY– groups in the percent of subjects with hC'SBA titers ≥ 1:4 for any of the four serogroups ($P > .05$ in each pairwise test; A, 41% vs. 50%; C, 93% vs. 91%; W, 79% vs. 65%; Y, 84% vs. 85%, respectively).

There were also no statistically significant differences between 10ACWY– and 5ACWY– groups in day 29 GMTs for any of the four serogroups ($P > .05$ in each pairwise test). For the W serogroup, the 13 vs. 8.07 comparison was **marginally statistically significant ($P = .054$)** in the 10ACWY– vs. 5ACWY– comparison.

Additionally, no statistically significant differences between the 10ACWY– and 5ACWY– groups were observed in the percent of subjects with hC'SBA titers ≥ 1:8 for any of the four serogroups ($P > .05$ in each pairwise test; A, 40% vs. 38%; C, 80% vs. 80%; W, 69% vs. 53%; Y, 75% vs. 78%, respectively). However, for serogroups W, the 69% vs. 53% comparison was **marginally statistically significant ($P = .060$)**.

The Menomune group exhibited an increased percentage of subjects with hC'SBA titers ≥ 1:4 relative to baseline for each serogroup (A, 36%; C, 45%; W, 60%; Y, 46%) and an increased percentage of subjects with hC'SBA titers ≥ 1:8 (A, 32%; C, 23%; W, 43%; Y, 36%). Menomune exhibited a 1.8- to 3.5-fold increase from baseline in GMT by day 29. In a post-hoc analysis, the percent of responders with hC'SBA titers ≥ 1: 4 and ≥ 1:8, and the GMTs, for the toddlers in the three Chiron MenACWY groups were statistically significantly higher than for the 3- to 5-year-olds in the Menomune group, for serogroups C, W, and Y (exception: serogroup W for the 5ACWY– group). For serogroup A, the point estimates for all comparisons were higher for the three Chiron MenACWY groups, but no statistically significant difference was observed in comparison to the Menomune group.

Safety results

Local and Systemic Reactions

These data were collected only in the three Chiron MenACWY vaccine groups.

Between 71% and 73% of subjects in the MenACWY groups experienced at least one solicited sign of reactogenicity during the 7-day reactogenicity monitoring period. Injection site reactions were observed in 31% to 37% of subjects, systemic reactions in 51% to 56%, and other reactions in 38% to 44%. The incidence of any reactogenicity signs was similar among the three MenACWY vaccine groups. There were no statistically significant differences between MenACWY vaccine groups in the incidence of any local, systemic, or other reaction within 7 days after study vaccination.

The time of first onset of injection site tenderness, erythema, and induration for all Chiron MenACWY subjects was within 3 days after vaccination. Tenderness subsided

for all but a few subjects by the day 4 to 7 interval. Erythema persisted during the day 4 to 7 interval for five 10ACWY– subjects, for one subject in the 5ACWY– groups, and for none of the subjects in the 5ACWY+ group. Induration persisted during the day 4 to 7 interval for 6, 5, and 1 subjects, respectively.

None of the MenACWY subjects exhibited the most extreme tenderness reaction ("cried when injection limb moved"). One subject in the 5ACWY+ group had erythema measured at 60 mm on day 2 (subject had 0 mm erythema before day 1 vaccination), which lasted one day and subsided to 0 mm from day 3 to day 7. This subject had no tenderness reactions and had induration measured at 10 mm on day 2 but did not exhibit any solicited systemic reactions. None of the MenACWY subjects had induration > 50 mm.

Although no difference was observed between the groups, the time of first onset of systemic reactions was most frequently within 3 days after vaccination for each MenACWY group. Typically, the first onset of a change in eating habits, sleepiness, and irritability was within the day 1 to 3 interval in approximately 70% to 75% of subjects and within the day 4 to 7 interval in the remaining 25% to 30% of the subjects. By contrast, the first onset of persistent crying, vomiting, diarrhea, and fever was more evenly spread throughout the 7-day monitoring interval. The incidence of each systemic reaction within the day 1 to 3 and day 4 to 7 intervals was similar among the MenACWY vaccine groups.

The time of first use of analgesic/antipyretic medication was similar between day 1 to 3 and day 4 to 7 intervals and among MenACWY groups. The frequency of use of analgesic/antipyretic medication was similar between day 1 to 3 and day 4 to 7 intervals for 10ACWY– and 5ACWY+ groups; approximately twice as many subjects in the 5ACWY– group received analgesic/antipyretic medication during the day 1 to 3 interval compared to the day 4 to 7 interval.

Other Adverse Events

These data were collected in all vaccine groups.

There were no deaths reported during or after the study.

Seven subjects experienced SAEs during the study, including three subjects in the 10ACWY– group, one subject each in the 5ACWY– and 5ACWY+ groups, and two subjects in the Menomune group. None of the SAEs was considered related to a study vaccine by the investigator.

The incidence of AEs in the Menomune and Chiron MenACWY groups could not be directly compared due to differences in the age groups and data collection methodology. Only SAEs and significant medical events were collected in the Menomune group. Menomune AE incidence was described separately.

None of the subjects were withdrawn from the study due to adverse events.

At least one AE was experienced by 59%, 65%, and 61% of Chiron MenACWY subjects in 10ACWY–, 5ACWY–, and 5ACWY+ groups, respectively. More Chiron

MenACWY subjects exhibited MedDRA-categorized respiratory, gastrointestinal, and general AEs than any other AEs during the study. The incidence of individual AEs experienced by subjects in MenACWY groups, regardless of causality, was highest for otitis media (6% to 11% of subjects in the three MenACWY groups), teething (8% to 14%), upper respiratory tract infection (4% to 10%), cough (4% to 11%), pyrexia (2% to 7%), gastroenteritis (4% to 9%), nasal congestion (1% to 8%), rhinorrhea (5% to 7%), and diarrhea (2% to 9%). The incidence of AEs from all causes was similar among the MenACWY vaccine groups. The percent of MenACWY subjects with one or more AEs ranged from 33% to 35% during the interval from 1 to 7 days after vaccination and from 38% to 41% during the interval from 8 days after vaccination to study termination.

No more than 4% to 5% of MenACWY subjects experienced AEs that were severe in intensity according to the investigator. None of the severe AEs occurred within the first 7 days after vaccination, and none were considered related to study vaccines by the investigator.

Eighteen (18) of 235 MenACWY subjects (8%) were considered by the investigator to have experienced AEs possibly or probably related to study vaccines. Pyrexia, diarrhea, irritability, and decreased appetite were the only MenACWY-related AEs reported for more than one subject. These events occurred within the first 7 days after vaccination in all but three of the subjects. None of the related AEs was severe in intensity.

An unexpected adverse event of note was identified in a subject in the 5ACWY+ group. The subject was without complaint at a routine clinic visit on day 59 but noted to have significant bruising on the arms and legs. A complete blood count indicated a platelet count of 19000 per μL with other cell lines normal, consistent with Idiopathic Thrombocytopenic Purpura (ITP). Subsequent blood tests showed increasing platelet counts with resolution of ITP per subject's physician. On day 29, the subject had received routine immunizations including measles, mumps and rubella (MMR), varicella zoster virus (VZV), *Haemophilus influenzae* type B (Hib), and diphtheria, tetanus, and acellular pertussis (DTaP). The investigator judged the event of moderate severity and possibly related to study vaccine. Based on previously identified association and temporal relationship, the most likely precipitant of the ITP was the MMR vaccine, but relationship to MenACWY could not be conclusively excluded.

In the Menomune group, at least one AE was experienced by 35% of the subjects. The incidence of individual AEs experienced by Menomune subjects, regardless of causality, was highest for otitis media (11% of Menomune subjects), upper respiratory tract infection (5%), and pyrexia (4%). Eight percent of Menomune subjects experienced at least one severe AE.

Conclusions

The presence of aluminum phosphate adjuvant in Chiron MenACWY 5 μg vaccine did not significantly increase the percentage of responders (hC'SBA ≥ 1:4) to any of the four antigen serogroups at day 29 (approximately one month after vaccination), compared to the non-adjuvanted MenACWY 5 μg group. Presence of the adjuvant also

did not significantly increase hC'SBA GMTs to any serogroup, although there was a marginally significant trend toward a greater response to serogroup W in adjuvanted than in non-adjuvanted 5 μg groups. Presence of the adjuvant did not significantly increase the percentage of subjects with hC'SBA titers ≥ 1:8 to serogroups A, C, and Y; however, the percent of subjects with hC'SBA titer ≥ 1:8 was statistically higher for the adjuvanted than the non-adjuvanted 5 μg group.

Non-adjuvanted 10 μg and adjuvanted 5 μg MenACWY groups were virtually identical in the percentage of responders (both hC'SBA ≥ 1:4 and ≥ 1:8) and in hC'SBA GMT to each of the four serogroups; no trends were apparent that might suggest a difference in response to any serogroup.

Non-adjuvanted 10 μg and non-adjuvanted 5 μg MenACWY groups were also virtually identical in the percentage of responders (both hC'SBA ≥ 1:4 and ≥ 1:8) and in hC'SBA GMT to serogroups A, C, and Y. However, there was a marginally significant trend toward a greater response to serogroup W in the 10 μg non-adjuvanted group than in 5 μg non-adjuvanted group in all three measures of immunogenicity.

Chiron MenACWY vaccines in 10 μg non-adjuvanted, 5 μg non-adjuvanted, and 5 μg adjuvanted formulations were similarly well-tolerated by 12- to 16-month old subjects during the present study.

Post-hoc analysis revealed that immune responses, as measured by percent of responders with hSBA titers ≥ 1: 4 and ≥ 1:8, and by GMTs at day 29, were higher in each of the Chiron MenACWY groups (10ACWY–, 5ACWY–, and 5ACWY+) compared to Menomune, for all four serogroups, and most of the differences were statistically significant. The largest differences (highly statistically significant: $P < .001$ for all comparisons) were observed for serogroups C and Y.

Table 2-1 Time and Events: Groups I to III

Visit Number **Study Day**	**1** **1**	**☎** **3**	**☎** **8**	**2** **29**	**☎** **180**
(Range)	(1)	(2 to 4 days after Visit 1)	(7 to 11 days after Visit 1)	(28 to 34 days after Visit 1)	(165 to 195 days after Visit 1)
Procedures					
Obtain Informed Consent	X				
Medical History	X				
Physical Examination[a]	X			X	
Review Vaccination History[b]	X				
Obtain Blood Sample	X			X	
Administer Study Vaccine[c]	X				
Injection-site Examination	X			X	
Assess Local & Systemic Reactions[d,e]	X	X	X	X	
Concomitant Medications[f]	X	X	X	X	
Adverse Events[g]	X	X	X	X	X
Termination					X

Note: day 1 is defined as day of study vaccination.

[a] The physical examinations at visits 1 and 2 (study days 1 and 29) were to be performed by a study physician or a study nurse designate.

[b] This was a review of the subject's complete vaccination history documented by medical record.

[c] The study vaccine (**MenACWY**) was administered intramuscularly into the subject's **left deltoid**.

[d] Local and systemic reactions were noted by subject's parent or guardian in the subject "diary", a diary card, daily on study days 1 through 7; this diary card was reviewed during the follow-up phone interviews and was collected at visit 2.

[e] Data on local and systemic reactions were collected for all subjects at 30 minutes postvaccination.

[f] Collect data on all concomitant medications (prescription and non-prescription) 7 days following vaccination; collect prescription medications only from day 8 through study termination.

[g] This included all adverse events that occurred within 7 days after the study vaccination (study days 1 through 7). In addition, information regarding any serious adverse event, any event requiring a physician visit through visit 2, or any event resulting in a subject's early termination any time during the subject's study participation must be obtained. A 6-month follow-up call was made to assess the occurrence of SAEs and significant medical events (e.g., hospitalizations, emergency room [ER] visits) requiring a physician visit (excluding visits for routine medical care, immunization, or common acute conditions as specified in section 9.1 of the protocol).

Table 2-2 Time and Events: Group IV

Visit Number **Study Day**	**1** **1**	**2** **29**	**☎** **180**
(Range)	(1)	(28 to 34 days after Visit 1)	(165 to 195 days after Visit 1)
Procedures			
Obtain Informed Consent	X		
Medical History	X		
Physical Examination[a]	X	X	
Review Vaccination History[b]	X		
Obtain Blood Sample	X	X	
Administer Study Vaccine[c]	X		
Injection-site Examination[d]	X	X	
Concomitant Medications[e]	X	X	
Adverse Events[f]	X	X	X
Termination			X

Note: day 1 was defined as day of study vaccination.

[a] The physical examinations at visits 1 and 2 (study days 1 and 29) were performed by a study physician or a study nurse designate.

[b] This was a review of the subject's complete vaccination history documented by medical record.

[c] The study vaccine, licensed meningococcal vaccine, **Menomune**, was administered subcutaneously into the subject's **left upper arm**.

[d] Subjects in group IV were observed in the clinic for 30 minutes following immunization.

[e] Collect data on concomitant medications (prescription only) through the entire study period.

[f] Collect information regarding any serious adverse event, any event requiring a physician visit through visit 2, or any event resulting in a subject's early termination any time during the subject's study participation. A 6-month follow-up call was made to assess the occurrence of SAEs and significant medical events (e.g., hospitalizations, ER visits) requiring a physician visit (excluding visits for routine medical care, immunization, or common acute conditions as specified in section 9.1 of the protocol).

Table 2-3 Primary Immunogenicity Variable: Percent of Responders (hC'SBA Titers ≥ 1:4)

Sero-group	Day	hC'SBA	Vaccine Group			
			Group I 10ACWY–	Group II 5ACWY–	Group III 5ACWY+	Group IV Menomune
A	**1**	n (%) ≥ 1:4 95% CI (%) N	0 0 – 5 70	1 (2) 0.038 – 8 66	2 (3) 0 – 11 62	1 (1) 0.037 – 8 69
	29	n (%) ≥ 1:4 95% CI (%) N	**29 (41)** 30 – 54 70	**33 (50)** 37 – 63 66	**28 (45)** 32 – 58 62	**25 (36)** 25 – 49 69
C	**1**	n (%) ≥ 1:4 95% CI (%) N	2 (3) 0 – 10 70	0 0 – 5 66	0 0 – 6 62	6 (9) 3 – 18 69
	29	n (%) ≥ 1:4 95% CI (%) N	**65[b] (93)** 84 – 98 70	**60[c] (91)** 81 – 97 66	**55[d] (89)** 78 – 95 62	**31[bcd] (45)** 33 – 57 69
W	**1**	n (%) ≥ 1:4 95% CI (%) N	1 (1) 0.036 – 8 70	1 (2) 0.038 – 8 66	2 (3) 0 – 11 62	6 (9) 3 – 18 67
	29	n (%) ≥ 1:4 95% CI (%) N	**55[ae] (79)** 67 – 87 70	**43[a] (65)** 52 – 76 66	**48[f] (77)** 65 – 87 62	**40[ef] (60)** 47 – 72 67
Y	**1**	n (%) ≥ 1:4 95% CI (%) N	0 0 – 5 67	3 (5) 1 – 13 65	3 (5) 1 – 14 59	9 (13) 6 – 24 67
	29	n (%) ≥ 1:4 95% CI (%) N	**56[g] (84)** 73 – 92 67	**55[h] (85)** 74 – 92 65	**48[i] (81)** 69 – 90 59	**31[ghi] (46)** 34 – 59 67

Source: [Table 11.4.1.1-1] Tables 14.2.1.1 and 14.2.1.1.1. Results by center in Table 14.2.1.1.2.
Individual subject results: Appendix 16.2.6.1. Post-hoc analyses: Table 14.2.1.1.3.

Primary immunogenicity analysis: II vs. III: $P > .10$ for serogroups A, C, W, and Y.

Secondary immunogenicity analyses:

[a] I vs. II: $P = .079$ for serogroup W; $P > .10$ for serogroups A, C, Y. I vs. III: $P > .10$ for serogroups A, C, W, and Y.

Post-hoc analyses:

[b] $P < .001$; [c] $P < .001$; [d] $P < .001$; [e] $P = .015$; [f] $P < .027$; [g] $P < .001$; [h] $P < .001$; [i] $P < .001$.

Table 2-4 Secondary Immunogenicity Variable: Geometric Mean hC'SBA Titers

Sero-group	Day	hC'SBA	Vaccine Group			
			Group I 10ACWY–	**Group II 5ACWY–**	**Group III 5ACWY+**	**Group IV Menomune**
A	**1**	GMT 95% CI N	2.03 1.96 – 2.11 70	2.07 1.99 – 2.15 66	2.12 2.04 – 2.21 62	2.07 1.97 – 2.17 69
	29	GMT 95% CI N	**5.84** 4.13 – 8.26 70	**5.92** 4.15 – 8.45 66	**7.15** 4.94 – 10 62	**7.18** 4.53 – 11 69
C	**1**	GMT 95% CI N	2.08 1.96 – 2.21 70	1.99 1.87 – 2.11 66	1.99 1.87 – 2.12 62	2.22 2.06 – 2.41 69
	29	GMT 95% CI N	**21**[c] 15 – 29 70	**20**[d] 15 – 28 66	**20**[e] 14 – 28 62	**3.98**[cde] 2.6 – 6.08 69
W	**1**	GMT 95% CI N	2.03 1.87 – 2.2 70	2.01 1.85 – 2.19 66	2.05 1.88 – 2.24 62	2.32 2.08 – 2.59 67
	29	GMT 95% CI N	**13**[bf] 8.87 – 19 70	**8.07**[ab] 5.53 – 12 66	**13**[ag] 8.82 – 19 62	**5.72**[fg] 3.48 – 9.4 67
Y	**1**	GMT 95% CI N	1.97 1.76 – 2.2 67	2.1 1.88 – 2.35 65	2.13 1.89 – 2.39 59	2.46 2.13 – 2.84 67
	29	GMT 95% CI N	**21**[h] 14 – 31 67	**20**[i] 14 – 30 65	**15**[j] 9.6 – 22 59	**5.68**[hij] 3.39 – 9.52 67

Source: [Table 11.4.1.2.1-1] Tables 14.2.1.3 and 14.2.1.3.1. Results by center in Table 14.2.1.3.2.
Individual subject results: Appendix 16.2.6.1. Post-hoc analyses: Table 14.2.1.3.4.

Secondary immunogenicity analyses:

[a] II vs. III: $P = .054$ for serogroup W; $P > .10$ for serogroups A, C, Y. [b] I vs. II: $P = .054$ for serogroup W; $P > .10$ for serogroups A, C, Y.

I vs. III: $P > .10$ for serogroups A, C, W, and Y.

Post-hoc analyses:

[c] $P < .001$; [d] $P < .001$; [e] $P < .001$; [f] $P = .005$; [g] $P = .005$; [h] $P < .001$; [i] $P < .001$; [j] $P < .001$.

Table 2-5 Secondary Immunogenicity Variable: Percent of Subjects with hC'SBA Titers ≥ 1:8

Sero-group	Day	hC'SBA	Vaccine Group			
			Group I 10ACWY–	**Group II 5ACWY–**	**Group III 5ACWY+**	**Group IV Menomune**
A	**1**	n (%) ≥ 1:8 95% CI (%) N	0 0 – 5 70	0 0 – 5 66	1 (2) 0.041 – 9 62	0 0 – 5 69
	29	n (%) ≥ 1:8 95% CI (%) N	**28 (40)** 28 – 52 70	**25 (38)** 26 – 51 66	**25 (40)** 28 – 54 62	**22 (32)** 21 – 44 69
C	**1**	n (%) ≥ 1:8 95% CI (%) N	1 (1) 0.036 – 8 70	0 0 – 5 66	0 0 – 6 62	1 (1) 0.037 – 8 69
	29	n (%) ≥ 1:8 95% CI (%) N	**56[c] (80)** 69 – 89 70	**53[d] (80)** 69 – 89 66	**50[e] (81)** 69 – 90 62	**16[cde] (23)** 14 – 35 69
W	**1**	n (%) ≥ 1:8 95% CI (%) N	1 (1) 0.036 – 8 70	0 0 – 5 66	0 0 – 6 62	4 (6) 2 – 15 67
	29	n (%) ≥ 1:8 95% CI (%) N	**48 (69)[bf]** 56 – 79 70	**35[ab] (53)** 40 – 65 66	**44[ag] (71)** 58 – 82 62	**29[fg] (43)** 31 – 56 67
Y	**1**	n (%) ≥ 1:8 95% CI (%) N	0 0 – 5 67	2 (3) 0 – 11 65	1 (2) 0.043 – 9 59	7 (10) 4 – 20 67
	29	n (%) ≥ 1:8 95% CI (%) N	**50 (75)** 63 – 84 67	**51 (78)** 67 – 88 65	**40 (68)** 54 – 79 59	**24 (36)** 24 – 48 67

Source: [Table 11.4.1.2.5-1] Tables 14.2.1.2 and 14.2.1.2.1. Results by center in Table 14.2.1.2.2. Individual subject results: Appendix 16.2.6.1. Post-hoc analyses: Table 14.2.1.2.3.

Secondary immunogenicity analysis:

[a] II vs. III: $P = .033$ for serogroup W; $P > .10$ for serogroups A, C, Y. [b] I vs. II: $P = .060$ for serogroup W; $P > .10$ for serogroups A, C, Y. I vs. III: $P > .10$ for serogroups A, C, W, and Y.

Post-hoc analyses:

[c] $P < .001$; [d] $P < .001$; [e] $P < .001$; [f] $P = .002$; [g] $P < .001$; [h] $P < .001$; [i] $P < .001$; [j] $P < .001$.

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S r.l Via Fiorentina, 1 53100 Siena, Italy	Individual Study Table Referring to Part [ ] of the Dossier Volume: Page: Study number: V59P5	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate		

Title of Study: A Phase II, Randomized, Open label, Controlled, Multicenter Study to Evaluate the Safety, Immunogenicity, and Induction of Immunological Memory after Two or Three Doses of Novartis Meningococcal ACWY Conjugate Vaccine Administered to Healthy Infants at 2, 3, 4 or 2, 4, and 6 Months of Age

Protocol Number: V59P5

Investigators: Andrew J. Pollard, FRCPCH, Scott Halperin, MD, Simon Dobson, MD

Study Centers: Oxford Vaccine Group, Oxford University Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK; Clinical Trials Research Center, Dalhousie University, IWK Health Centre, Halifax, Canada; Vaccine Evaluation Center, Department of Pediatrics, British Columbia's Children's Hospital, Vancouver, Canada.

Publication (reference): Immunogenicity of a TetravalentMeningococcal Glycoconjugate Vaccine in Infants: A Randomized Controlled Trial. JAMA. 2008;299(2):173-184.

Study Period: (date of first enrollment) 01 SEP 04 (date of last completed) 02 OCT 06	**Phase of Development**: Phase 2

Objectives:

Immunogenicity Objectives

Primary:

To assess the immunogenicity of three doses of Novartis MenACWY Ad+ conjugate vaccine given at 2, 3, and 4 or 2, 4, and 6 months of age, as measured by the percentage of subjects with hSBA ≥ 1:4, against *N meningitidis* serogroups A, C, W, and Y.

Secondary:

- To assess the immunogenicity of three doses of Novartis MenACWY Ad+ conjugate vaccine given at 2, 3, and 4 or 2, 4, and 6 months of age, as measured by hSBA geometric mean titer (GMT) and hSBA ≥ 1:8 against *N meningitidis* serogroups A, C, W, and Y;
- To assess the immunogenicity of two doses of Novartis MenACWY Ad+ and Novartis MenACWY Ad- conjugate vaccines given at 2 and 4 months of age, as measured by hSBA ≥ 1:4,

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	Study number: V59P5	

hSBA ≥ 1:8, and hSBA GMT, against *N meningitidis* serogroups A, C, W, and Y;

- To assess the immunogenicity of a booster dose of Novartis MenACWY Ad+ or Novartis MenACWY Ad- conjugate vaccines given at 12 months of age in a subgroup of subjects receiving either two or three doses of Novartis MenACWY Ad+, or two doses of Novartis MenACWY Ad- conjugate vaccine, as measured by hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT, against *N meningitidis* serogroups A, C, W, and Y;
- To assess the persistence of antibodies at 12 months of age in subjects who previously received two doses of Novartis MenACWY Ad+, or Novartis MenACWY Ad- conjugate vaccine, or Novartis Menjugate ™ vaccine, as measured by hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT, against *N meningitidis* serogroups A, C, W, and Y;
- To assess the persistence of antibodies at 12 months of age in subjects who previously received three doses of Novartis MenACWY Ad+ conjugate vaccine, as measured by hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT, against *N meningitidis* serogroups A, C, W, and Y;
- To assess the induction of immunological memory by challenge with a reduced dose of licensed Meningococcal ACWY polysaccharide (PS) vaccine, Menomune ™, given at 12 months of age in a subgroup of subjects who previously received three doses of Novartis MenACWY Ad+ conjugate vaccine, as measured by hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT, directed against *N meningitidis* serogroups A, C, W, and Y (Group IV);
- To assess the induction of immunological memory by challenge with a reduced dose of licensed Meningococcal ACWY PS vaccine given at 12 months of age in a subgroup of subjects who previously received two doses of Novartis MenACWY Ad+ or Novartis MenACWY Ad- conjugate vaccine as measured by hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT, directed against *N meningitidis* serogroups A, C, W, and Y (Groups V and VII);
- To assess the immunogenicity of Novartis MenACWY Ad+ conjugate vaccine after a three-dose regimen in comparison to the immunogenicity of Novartis MenACWY Ad+ conjugate vaccine after a two-dose regimen, as measured by hSBA ≥ 1:4 and hSBA ≥ 1:8, directed against *N meningitidis* serogroups A, C, W, and Y;
- To assess the memory response of Novartis MenACWY Ad+ conjugate vaccine after a three-dose regimen in comparison to the memory response of Novartis MenACWY Ad+ conjugate vaccine after a two-dose regimen, as measured by hSBA ≥ 1:4 and hSBA ≥ 1:8, directed against *N meningitidis* serogroups A, C, W, and Y (Groups IV and V);
- To assess the immunogenicity of routine vaccines when given concomitantly to Novartis MenACWY Ad+ or Novartis MenACWY Ad- conjugate vaccines with the evaluation of titers

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	Study number: V59P5	

against Hib, diphtheria, tetanus, pertussis as the first priority, followed by *Pneumococcus*, polio, Hepatitis B, and MMR (measles, mumps, and rubella) depending on the availability of sera);

- To measure the immunogenicity of Novartis MenACWY Ad+ or Novartis MenACWY Ad- conjugate vaccine (containing 5 µg of MenC oligosaccharide), and that of Novartis Menjugate™ (containing 10 µg of MenC oligosaccharide), when administered in a two-dose regimen, as measured by hSBA ≥ 1:4 and hSBA ≥ 1:8, directed against *N meningitidis* serogroup C.

Safety Objectives

- To evaluate the safety and tolerability of Novartis MenACWY Ad+ conjugate vaccine when given concomitantly with other licensed pediatric vaccines at 2, 3, and 4 or 2, 4, and 6 months of age;
- To evaluate the safety and tolerability of Novartis MenACWY Ad- conjugate vaccine when given concomitantly with other licensed pediatric vaccines at 2 and 4 months of age;
- To evaluate the safety and tolerability of Novartis MenACWY Ad+ and Novartis MenACWY Ad- conjugate vaccine when given concomitantly with other licensed pediatric vaccines at 12 months of age.

Methodology: This was a phase 2, open-label, multicenter, randomized, controlled study in healthy infants in the United Kingdom (UK) and Canada. Subjects were to be included in the study if in good health as judged by physical examination and medical history, and if they met all inclusion criteria and no exclusion criteria. Approximately 585 infants who were 2 months old (55-89 days inclusive) at the time of enrollment were to be enrolled and randomized in two phases of the study: Protocol Amendment 3 was implemented to get confirmatory data on the final vaccine formulation without adjuvant. To this effect, two new study groups—Group VI in the UK, and Group VII in Canada—were to be included as the second phase of the study. These groups were to receive Novartis MenACWY conjugate vaccine formulated without the adjuvant (Novartis MenACWY Ad-) to be given concomitantly with the routine infant vaccination schedule.

Phase 1: 405 subjects were randomized in a 2:2:1:2:2 ratio to one of five vaccination groups (Groups I-V) to receive either two or three doses of MenACWY Ad+ conjugate vaccine (Groups I-II, IV-V), or two doses of Novartis Menjugate (Group III). At 12 to 14 months of age, subjects belonging to Groups I, II, and III (in UK) received a booster dose of MenACWY Ad+ conjugate vaccine. In Canada, subjects belonging to Group V were randomized in a 1:1 ratio to receive either one booster dose of MenACWY Ad+ conjugate vaccine or a challenge dose (reduced to one fifth the usual dose) of a Men PS vaccine. Approximately 50% of subjects belonging to Group IV received a reduced dose (one fifth) of Men PS vaccine.

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Phase 2: 90 subjects in each country were assigned to one vaccination group: Group VI in UK received two doses (at 2 and 4 months) of MenACWY Ad- conjugate vaccine concomitantly with DTaPHibIPV vaccine, and Group VII in Canada received two doses (at 2 and 4 months) of MenACWY Ad- conjugate vaccine concomitantly with diphtheria, tetanus, acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), inactivated poliovirus (IPV), hepatitis B virus vaccine (HBV), and Prevnar ™ vaccines. At 12 to 14 months of age, subjects belonging to Group VI received a booster dose of MenACWY Ad- conjugate vaccine, and subjects belonging to Group VII were randomized in a 1:1 ratio to receive either one booster dose of MenACWY Ad- conjugate vaccine or a challenge-reduced dose (one fifth) of a Men PS vaccine.

All subjects also received concomitant vaccinations with age-appropriate, country-specific, recommended vaccines at separate injection sites.

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Country	Group Type of conjugate vaccine	Months of age	No. subjects	Type of vaccine (12 months of age)	No. subjects
UK Tot=315	I MenACWY Ad+	2, 3, and 4	90	MenACWY Ad+	90
	II MenACWY Ad+	2, 4	90	MenACWY Ad+	90
	III Menjugate®	2, 4	45	MenACWY Ad+	45
	VI MenACWY Ad-	2, 4	90	MenACWY Ad-	90
Canada Tot=270	IV MenACWY Ad+	2, 4, and 6	90	PS	45*
	V MenACWY Ad+	2, 4	90	MenACWY Ad+	45
				PS	45
	VII MenACWY Ad-	2, 4	90	MenACWY Ad-	45
				PS	45

The remaining 45 subjects in Group IV, who did not receive PS vaccine, received concomitant vaccines.

Appropriate recommended vaccines (e.g., MMR in the UK, and Varicella in Canada) were offered but not included in the study evaluation, with the exception of MMR and Prevnar in Canada, which were administered at 12 months of age during the course of the trial.

All subjects were observed for at least 15 to 30 minutes following each immunization to assess for immediate hypersensitivity reactions. The parents/legal guardians of the subjects were instructed to complete a diary card for both local (i.e., tenderness, erythema, induration), and systemic reactions (i.e., change in eating habits, sleepiness, persistent crying lasting ≥ 3 hours, vomiting, diarrhea, and irritability) for 7 days following each vaccination. During this period, axillary temperature was also recorded daily at the same time of the day, whenever possible.

Subjects' health status was assessed by telephone call 2 days (day 3, window +2 days), and 7 days (day 8, window +4 days) after each vaccination. The diary cards were collected, and the data were recorded and reconciled, during the following site visit.

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All adverse events (AEs) were collected for 7 days following each vaccination, after which only serious adverse events (SAE), and adverse events necessitating a physician's visit and/or resulting in premature withdrawal of subjects from the study were collected, and recorded by study personnel until the next study visit (applicable to visit 1 to visit 4, and visit 5 to visit 6). Between visit 4 and visit 5, a monthly telephone call was made to check for the subject's health, and any SAE was recorded. A follow-up phone call to assess the health status of the subject was performed 6 months after the last study visit. During this phone call, information about SAEs and any medically significant AEs requiring a physician visit or leading to an Emergency Room visit were recorded (not recorded were preplanned visits, medical office visits for routine medical care, and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries).

Immunogenicity was assessed by evaluating serum antibody responses to *N meningitidis* serogroup A, C, W, and Y by measuring bactericidal antibody titers using human complement (hSBA) as primary bactericidal antibody assay. In case a sufficient amount of serum could be obtained from the subject, further serological tests on the response to the components of the concomitantly administered routine vaccine were performed if appropriate; evaluation of titers against Hib, diphtheria, tetanus, and pertussis were the first priority, followed by *Pneumococcus*, polio, Hepatitis B, and MMR (as appropriate).

Number of Subjects (planned and analyzed): 585 subjects were planned. A total of 553 subjects were analyzed, including 209 subjects in groups I, II, and III (UK), 173 subjects in groups IV and V (Canada), 84 subjects in group VI (UK), and 87 subjects in group VII (Canada).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion criteria:

Individuals eligible for enrollment in this study were male, and female infants:

- Who were healthy 2-month old infants (55-89 days, inclusive) born after full term pregnancy with an estimated gestational age ≥ 37 weeks, and a birth weight ≥ 2.5 kg;
- For whom a parent/legal guardian has given written informed consent after the nature of the study has been explained;
- Who were available for all the visits scheduled in the study;
- Who were in good health as determined by:
  - Medical history;
  - Physical examination;
  - Clinical judgment of the investigator.

Exclusion criteria:

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Ineligible for the study were infants:

- Whose parents/legal guardians were unwilling, or unable to give written informed consent for the subject to participate in the study;
- Who previously received any meningococcal vaccine;
- Who received prior vaccination with D, T, P (acellular, or whole cell), IPV, or OPV, HBV, *H influenzae* type b (Hib), or *Pneumococcus*;
- Who had a previously ascertained or suspected disease caused by *N meningitidis, C diphtheriae, C tetani*, *Poliovirus*, Hepatitis B, Hib, *Pneumococcus*, or *B pertussis* (history of laboratory-confirmed or clinical condition of spasmodic cough for a period ≥ 2 weeks associated with apnea or whooping cough);
- Who had household contact with and/or intimate exposure to an individual with laboratory-confirmed *N meningitidis* (serogroups A, C, W-135, or Y), *B pertussis*, Hib, *C diphtheriae*, Polio, or pneumococcal infection since birth;
- Who had a history of any anaphylactic shock, asthma, urticaria, or other allergic reaction after previous vaccinations, or known hypersensitivity to any vaccine component;
- Who had experienced significant acute or chronic infection within the previous 7 days, or fever (≥ 38.0°C) within the previous 3 days;
- Who had any present, or suspected serious, acute (e.g., leukemia, lymphomas), or chronic disease (e.g., with signs of cardiac, renal failure, or severe malnutrition, or insulin-dependent diabetes); or progressive neurological disease; or a genetic anomaly or known cytogenic disorders (e.g., Downs syndrome);
- Who had a known or suspected autoimmune disease or impairment /alteration of immune function resulting from (for example):
  - receipt of any immunosuppressive therapy since birth;
  - receipt of immunostimulant since birth;
  - receipt of any systemic corticosteroid since birth.
- Who had a suspected or known HIV infection, or HIV-related disease;
- Who had ever received blood, blood products and/or plasma derivatives, or any parenteral immunoglobulin preparation;
- Who had a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
- Who had a history of seizure disorder:

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- Febrile seizure;
- Any other seizure disorder.

- Who had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (EXCEPTION: subjects who received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.] may be enrolled 7 days following the last dose);
- Who with their parents/legal guardians were planning to leave the area of the study site before the end of the study period;
- Who had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives;
- Who had taken any antipyretic medication in the previous 6 hours.

Test Product, Dose, Mode of Administration, Lot Number:

One dose of 0.5 mL of Novartis MenACWY conjugate vaccine was injected intramuscularly (IM) in the left deltoid. Novartis MenACWY Ad+ (with adjuvant) conjugate vaccine was injected in group I (at 2, 4, and 6, and at 12 months), group II (at 2, 4, and 12 months), group III (at 12 months), group IV (at 2, 4, and 6 months), and group V (at 2 and 4 months for all, and at 12 months in a subgroup). Novartis MenACWY Ad- (without adjuvant) conjugate vaccine was injected in group VI (2, 4, and 12 months), and group VII (at 2 and 4 months for all subjects, and at 12 months in a subgroup of subjects). The vaccines used in the United Kingdom and Canada were from identically manufactured lots; the trailing "A" was used for tracking purposes only. Batch lot numbers were the following:

	United Kingdom	**Canada**
MenACWY Ad+	**Lot number**	**Lot number**
Vial A (MenA)	563001011	563001011
Vial B (MenC, MenW, MenY)	U79P27D1A	U79P27D1
MenACWY Ad-	**Lot number**	**Lot number**
Vial A (MenA)	563001011	563001011
Vial B (MenC, MenW, MenY)	U79P27D1	U79P27D1A

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After reconstitution, Novartis MenACWY Ad+ conjugate vaccine had the following composition per 0.5 mL of injectable solution:

CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC; (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW; (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY; (b) (4) µg CRM_{197}
Aluminum phosphate	0.3 mg Al3+
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

CRM = cross-reactive material

After reconstitution, Novartis MenACWY Ad- conjugate vaccine has the following composition per 0.5 mL of injectable solution:

CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC; (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW; (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY; (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

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MenACWY polysaccharide vaccine Menomune (Aventis Pasteur Inc., Swiftwater, Pennsylvania) was reconstituted with the liquid diluent supplied. The vaccine included four meningococcal capsular polysaccharide serogroups (A, C, Y, and W_{135}).

One reduced dose (one fifth of the full dose content) of Menomune was injected subcutaneously (SC) into the anterolateral area of the right thigh at 12 months of age in group IV, and in subgroups of groups V and VII. After reconstitution, Menomune had the following composition per 0.5 mL of injectable solution:

Isolated product from each of groups A, C, Y, and W_{135}	50 µg
Lactose	2.5-5 mg
Sodium chloride	4.25-4.75 mg
Liquid diluent sterile water for injection	up to 0.5 mL

Concomitant vaccines:

DTP, Polio, Hib, HBV, MMR, varicella, and heptavalent pneumococcal vaccines were administered according to recommended vaccination schedule for infants and toddlers in UK and Canada.

In the UK

Pediacel (Aventis Pasteur MSD Ltd), a five-in-one vaccine (diphtheria, tetanus, five-component acellular pertussis, *H influenzae* type b, and inactivated polio (DTaP Hib IPV), was administered. All subjects of groups I, II, III, and VI received three doses of the vaccine (at 2, 3, and 4 months of age) IM in the anterolateral area of the left thigh. Each 0.5 mL contained *H influenzae* type b purified capsular polysaccharide (10 µg) covalently bound to tetanus protein (20 µg), pertussis toxoid (20 µg), filamentous hemagglutinin (FHA; 20 µg), agglutinogens types 2 and 3 (5 µg), pertactin (3 µg), diphtheria toxoid (15 Lf), tetanus toxoid (5 Lf), and purified inactivated poliomyelitis vaccine (Type 1 Mahoney; Type 2 M.E.F.1; Type 3 Saukett).

In Canada

Pentacel ™ (Aventis Pasteur MSD Ltd), a five-in-one vaccine, is a co-marketing of two vaccines—Quadracel ™ and Act-Hib ™ (Aventis Pasteur MSD Ltd). Act-Hib (lyophilized) was reconstituted immediately prior to vaccination with Quadracel (liquid). All subjects of groups IV, V, and VII received three doses of the vaccine (at 2, 4, and 6 months of age) IM into the anterolateral area of the left thigh. One dose of Act-Hib contained *H influenzae* type b purified capsular polysaccharide (15 µg) covalently bound to tetanus protein (24 µg). Each 0.5 mL dose of Quadracel contained pertussis toxoid (20 µg), filamentous hemagglutinin (20 µg), agglutinogens types 2 and 3 (5 µg), pertactin (3 µg), diphtheria toxoid (15 Lf), tetanus toxoid (5 Lf), and purified inactivated poliomyelitis vaccine (Type 1 Mahoney; Type 2

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M.E.F.1; Type 3 Saukett).

Recombivax® (Merck & Co., Inc) is a monovalent recombinant DNA hepatitis B vaccine. All subjects of groups IV, V, and VII received three doses of the vaccine (at 2, 4, and 6 months of age) IM into the anterolateral area of the left thigh. Each 0.5-mL dose contained hepatitis B surface antigen (HBsAg; 5 µg) adsorbed on aluminum (0.5 mg) without preservative.

Prevnar® (Wyeth Vaccines). Each 0.5-mL dose contained pneumococcal polysaccharide serotypes 4, 9V, 14, 18C, 19F, 23F (2 µg each), and 6B (4 µg) conjugated to the CRM_{197} carrier protein, and adsorbed on aluminum phosphate (0.5 mg). All subjects of groups IV, V, and VII received at least two doses of the vaccine at 2 and 4 months of age (third and fourth doses pending availability of the product in the market at 6 and 12 months of age) IM into the anterolateral area of the left thigh.

MMR® II (measles, mumps, and rubella; Merck Frosst Canada & Company). Each 0.5 mL dose of the reconstituted vaccine contained attenuated measles virus (≥ 1000 CCID50), mumps virus (≥ 5000 CCID50), and rubella virus (≥ 1000 CCID50).

All subjects of groups IV, V, and VII received one dose of the vaccine at 12 months of age subcutaneously into the left arm.

Duration of Study: The planned duration of the study was 22 months, with each subject participating for a maximum of 17 months.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Novartis Men C conjugated vaccine, Menjugate, was obtained by extemporaneous mixing just prior to injection of the lyophilized Men C component to be resuspended with the saline solvent (aluminum hydroxide suspension) supplied. One 0.5 mL dose of Menjugate was injected IM in the anterolateral area of the right thigh at 2 and 4 months of age in group III. After reconstitution, Menjugate had the following composition per 0.5 mL of injectable solution:

CRM_{197}-MenC conjugate	10 µg MenC oligosaccharide, 12.5-25.0 µg CRM_{197}
Aluminum hydroxide	1.0 mg
Sodium chloride	3.5 mg
Mannitol	7.3 mg
Sodium phosphate buffer (pH [(b) (4)]	(b) (4)

Criteria for Evaluation:

Immunogenicity

The functional bactericidal antibody titers against each serogroup were measured using human serum

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bactericidal assay (hSBA) in the presence of human complement, and expressed as anti-*N meningitidis* serogroup A, C, W, and Y hSBA geometric mean titers (GMTs), and percentage of subjects having hSBA ≥ 1:4 and ≥ 1:8.

Further analyses were performed with rabbit SBA (rSBA) in subgroups of subjects, and expressed as anti-*N meningitidis* serogroup A, C, W, and Y rSBA GMTs, percentage of responders (defined as having rSBA ≥ 1:8), and percentage of subjects with at least a 4-fold increase in titer.

Additional assays (e.g., ELISA) to further characterize the immune response to MenACWY vaccine were permitted by protocol, as appropriate.

Immunogenicity variables for assessing the immune response of concomitant vaccines were as follows:

- Percentage of subjects with anti- polyribosylribitol phosphate (PRP) titer ≥ 0.15 µg/mL, and ≥ 1.0 µg/mL;
- ELISA GMCs for anti-PRP titer;
- Percentage of subjects achieving a 4-fold increase in the antibody titer, or a postimmunization titer > 50 for at least one of the three pertussis antigens (PT, FHA, and pertactin);
- ELISA GMCs for anti-PT, anti-FHA, and anti-pertactin titers;
- Percentage of subjects with an anti-tetanus titer ≥ 0.1 IU/mL and ≥ 1.0 µg/mL;
- ELISA GMCs for anti-tetanus titer;
- Percentage of subjects with anti-diphtheria titer ≥ 0.1 IU/mL and ≥ 1.0 µg/mL;
- ELISA GMCs for anti-diphtheria titer;
- ELISA GMCs for anti-measles, anti-mumps, and anti-rubella titers;
- Percentage of subjects with NT titers ≥ 1:8;
- Percentage of subjects with anti-*S pneumoniae* titer ≥ 0.15 µg/mL (in addition, higher cutoffs were also used, if required);
- ELISA GMCs for anti-*S pneumoniae* titer;
- Percentage of subjects with anti-hepatitis B titer ≥ 10 IU/L.

Safety:
Safety was expressed as the number and percentage of subjects with reported local and systemic reactions, and the number (percentage) of subjects with reported SAEs and/or all AEs up to day 7 and/or AEs requiring a physician's visit and/or resulting in premature withdrawal from the study, per vaccination group.

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Statistical Methods:
Immunogenicity

The primary immunogenicity objective was to compare the percent of responders (defined as the percentage of subjects with hSBA titers ≥ 1:4) against *N meningitidis* serogroups A, C, W, and Y.

The null hypothesis associated with the primary immunogenicity objective was that, for at least one serogroup, the lower limit of the two-sided 95% CI of the underlying percentage of subjects with hSBA titer ≥ 1:4 at 1 month after the third dose was less than 70%.

Interim analysis of data from this trial was performed after immunogenicity and safety results were available following the primary vaccination.

Safety

All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 9.1, and grouped by MedDRA preferred terms into frequency tables according to MedDRA system-organ-class categories. Local and systemic reactions were evaluated by the chi-square or Fisher's exact test as appropriate for expected cell counts.

Summary and Conclusions:

Six hundred and one healthy subjects (less than 2 months of age)—315 from the UK and 286 from Canada—were randomized and enrolled at three study sites into seven groups. Groups I and II (UK) included 90 subjects each who received three and two doses of MenACWY Ad+ vaccine, respectively. Group III (UK) included 45 subjects who received two doses of Menjugate control vaccine. Groups IV and V (Canada) included 98 subjects who received three and two doses of MenACWY Ad+ vaccine, respectively. Groups VI (UK) and VII (Canada) included 90 subjects who received two doses of MenACWY Ad- vaccine.

Immunogenicity results

The null hypothesis for the primary objective of the study was rejected based on the finding that the lower limit of the two-sided 95% CI of the percentage of subjects with hSBA titers ≥ 1:4 exceeded the criterion 70% for MenACWY three-dose Ad+ regimens (vaccinations at 2, 3, and 4 months [93% to 97% in UK infants] and at 2, 4, and 6 months [81% to 99% in Canadian infants] of age) against at least one serogroup (the criterion 70% was met by both three-dose vaccine groups against all four serogroups). These findings supported the conclusion that both three-dose MenACWY Ad+ regimens were highly immunogenic against all four serogroups in UK and Canadian subjects during the study.

Secondary analyses showed that similar results were obtained in percentage of subjects with hSBA titers ≥ 1:8 and in GMTs, except against the A serogroup. Although a significant percentage of subjects had hSBA ≥ 1:4 at study entry, the data suggested that the source of this antibody was likely maternal, as

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subjects who received Menjugate had negative titers for W and Y serogroups at 5 months of age suggesting the natural decay of passively transferred antibodies.

Additional secondary analyses showed that two-dose MenACWY Ad+ and Ad- vaccines were immunogenic against all four serogroups, and there were no significant differences between UK Ad+ and Ad- groups and between Canadian Ad+ and Ad- groups. GMT and GMR results were similar to 1:4 and 1:8 results, except in the following instances: (a) GMTs were significantly higher in the Ad+ group than in the Ad- group in the UK against both the A and W serogroups, (b) GMTs were significantly lower in the Canadian Ad+ group than in the Ad- group against both the W and Y serogroups. Percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8, and GMTs and GMRs were generally substantially less against the A serogroup than against C, W, and Y serogroups.

A booster dose of MenACWY (Ad+/Ad-) increased the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 in UK two-dose MenACWY Ad+ and Ad- vaccine groups and the three-dose MenACWY Ad+ group. Antibody levels were high against all four serogroups at 1 month after the booster dose. At 1 month after the booster dose, there were no significant differences in percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 between the two- and three-dose groups. Additionally, in UK two-dose and three-dose groups GMTs significantly increased in response to the booster dose. GMTs were significantly greater in the three-dose UK group than in the two-dose UK MenACWY Ad+ groups against the A and Y serogroups and significantly greater than the two-dose UK MenACWY Ad- group against all four serogroups.

Persistence of the immune response at 12 months in both two-dose Ad+ and Ad- vaccine groups was lower against the A serogroup than against the C, W, and Y serogroups (percentages of Ad+ UK subjects with hSBA titers ≥ 1:4 at 12 months = 8%, 41%, 58%, and 51% against A, C, W, and Y serogroups; UK Ad- = 6%, 32%, 57%, and 56%, respectively). For Canadian groups, the percentages of subjects with hSBA titers ≥ 1:4 at 12 months were similar to those for UK groups (Canadian Ad+ = 8%, 48%, 64%, and 60%; Canadian Ad- = 5%, 35%, 75%, and 59%, respectively). As expected, Menjugate subjects in the UK had high levels of antibodies against the C serogroup but very low levels against A, W, and Y serogroups. Persistence in GMT results for Ad+, Ad-, and Menjugate vaccine groups mirrored results obtained at 1:4 and 1:8 dilutions.

Persistence was slightly lower in the three-dose UK MenACWY Ad+ vaccine group than in the Canadian Ad+ vaccine group against all four serogroups. Persistence at 12 months in both UK and Canadian Ad+ vaccine groups was lower against the A serogroup than against the C, W, and Y serogroups (percentages of UK Ad+ subjects with hSBA titers ≥ 1:4 at 12 months = 21%, 59%, 78%, and 85% against A, C, W, and Y serogroups; Canadian Ad+ = 35%, 75%, 89%, and 87%, respectively).

Reduced-dose polysaccharide challenge at 12 months of age resulted in high percentage of subjects achieving threshold bactericidal antibody levels at 1 month after challenge of Canadian subjects who

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previously received three doses of MenACWY Ad+ at 2, 4, and 6 months of age (range 89% to 98% of subjects with hSBA ≥ 1:4 among serogroups A, C, W, and Y). Results at hSBA ≥ 1:8 were similar, and hSBA GMTs also significantly increased for all serogroups but were lower against the A and C serogroups than against the W and Y serogroups.

Similarly, the reduced-dose polysaccharide challenge dose resulted in high percentage of subjects achieving threshold bactericidal antibody levels at 1 month after challenge of Canadian subjects who previously received two doses of MenACWY Ad+ or MenACWY Ad- at 2 and 4 months of age. hSBA GMTs also significantly increased for all serogroups but were lower against the A serogroup than against C, W, and Y serogroups. Except for the GMT response to serogroup A, there were no statistically significant differences in induction of memory response between Ad+ and Ad- groups.

Persistence (percentages of subjects with hSBA ≥ 1:4, 1:8, and GMTs) was generally higher when three doses of MenACWY Ad+ were given to UK subjects than when two doses were given. Percentages of subjects with hSBA ≥ 1:4 in the UK three-dose Ad+ vaccine group were 21%, 59%, 78%, and 85% against serogroups A, C, W, and Y, respectively; in the UK two-dose Ad+ group, results were 8%, 41%, 58%, and 51%. GMTs were slightly higher in the UK three-dose Ad+ group (3.02, 7.56, 15, and 18) than in the UK two-dose group (2.32, 5.04, 8.38, and 6.72). Results for Canadian three-dose vs. two-dose comparisons were similar (i.e., three doses were better than two doses).

With respect to the three vs. two dose primary vaccination series, the reduced-dose polysaccharide challenge at 12 months of age resulted in high percentage of subjects achieving threshold bactericidal antibody levels at 1 month after challenge of Canadian subjects who previously received three doses of MenACWY Ad+ at 2, 4, and 6 months of age (percentages of subjects with hSBA ≥ 1.4 = 89%, 95%, 98%, and 98% against A, C, W, and Y serogroups, respectively) or two doses of MenACWY at 2 and 4 months of age (78%, 95%, 98%, and 98%). There were no apparent differences between the three-dose and two-dose regimens against any of the four serogroups.

The immunogenicity of routine vaccines administered concomitantly with MenACWY Ad+ and Ad- vaccines, such as Pediacel in the UK and Pentacel, HBV and Prevnar in Canada, resulted in expected responses, as measured by titers against *H influenzae* serotype b (Hib), diphtheria, tetanus, *Pneumococcus*, and hepatitis B. At 1 month after primary vaccination, almost all subjects (≥ 99%) had antidiphtheria and antitetanus antibody titers ≥ 0.1 IU/mL in all vaccine groups. The immunogenicity of Hib vaccine, measured by the percentage of subjects with anti-PRP titer ≥ 0.15 µg/mL or ≥ 1.0 µg/mL, was at least 97% or 82%, respectively in all MenACWY groups where the assessment was done after the full 3 dose primary series. In Canada, immunogenicity (antipneumococcal titers ≥ 0.35 µg/mL) of a pentavalent pneumococcal conjugate vaccine given concomitantly with MenACWY Ad+ at 2, 4, and 6 months was at least 90% for each serotype. Pneumococcal immunogenicity after a booster dose given alone was at least 94% for all serotypes. Anti-HBV titers ≥ 10 IU/L were detected 97% of the Canadian

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three-dose Ad+ subjects. A substantially greater percentage of subjects showed antipneumococcal titers ≥ 0.35 µg/mL against pneumococcal polysaccharide serotypes 4, 9V, 14, 18C, 19F, 23F, and 6B (4 µg) after the booster vaccination versus the primary vaccination series.

The immunogenicity (hSBA ≥ 1:4) against serogroup C was significantly higher (98%) at 1 month after primary vaccination in the UK Menjugate group (containing 10 µg of MenC oligosaccharide) than that observed in both of the UK two-dose groups (Ad+, 84%; $P < .007$; Ad-, 86%, $P = .013$) (each containing 5 µg of MenC oligosaccharide).

Safety results

Local, systemic, and other reactions

After primary vaccination, 97% to 98% of subjects in the seven vaccine groups experienced at least one local, systemic, or other sign of reactogenicity, and the seven vaccine groups were similar in incidence of any local, systemic, or other sign of reactogenicity. After any of the first two or three vaccinations, erythema was the local reaction observed most frequently (MenACWY range = 71% to 83% of subjects; MenC = 76%) followed by tenderness (MenACWY = 33% to 47%, MenC = 40%), and induration (MenACWY = 18% to 44%; MenC = 27%).

Irritability was the most frequent systemic reaction (MenACWY = 68% to 82%; MenC = 69%) followed by sleepiness (MenACWY = 50% to 65%; MenC = 56%), change in eating habits (MenACWY = 22% to 36%; MenC = 20%), diarrhea (MenACWY = 18% to 32%; MenC = 27%), vomiting (MenACWY = 12% to 29%; MenC = 20%), persistent crying of at least 3 hours (MenACWY = 4% to 15%; MenC = 13%), and fever of at least 38ºC (MenACWY = 4% to 14%: MenC = 13%).

Thirty-nine percent to 62% of MenACWY subjects and 40% of MenC subjects took analgesic or antipyretic medication at least once after any of the first three vaccinations.

After MenACWY booster, polysaccharide challenge, and/or concomitant vaccinations at 12 months of age in Canada, the incidence of any local, systemic, or other reaction was also similar among the MenACWY groups except for the three-dose Ad+ group that only received concomitant vaccines (any reaction = 77% to 91%; Ad+ group 54%). The most frequently observed local, systemic, and other reactions were similar to those reported after primary vaccinations.

These results indicated that MenACWY and MenC vaccine groups were similar in incidence of local, systemic, and other reactions except for induration. Induration exhibited the widest disparity among the MenACWY groups (18% to 44%) and was due to the difference between the Canadian two-dose Ad+ and the UK two-dose Ad- groups, respectively.

Treatment-emergent adverse events

At least one AE was experienced by 89% and 85% of subjects in UK234+ and CA246+ groups, by 90% and 87% of subjects in UK24+ and CA24+ groups, and by 82% and 79% of subjects in UK24- and CA24-

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groups, respectively. In the control group (two doses of Menjugate), at least one AE was observed in 85% of subjects. Thus, the incidence of AEs from all causes was similar among the groups.

Overall, the highest incidence of AEs among MenACWY-treated subjects was in the MedDRA infections and infestations class (51% to 74%; MenC = 47%), followed by skin and subcutaneous tissue disorders (22% to 33%; MenC = 24%), gastrointestinal disorders (14% to 28%; MenC = 22%), and respiratory, thoracic, and mediastinal disorders (10% to 20%; MenC = 22%).

Individual AEs reported by the greatest percentage of subjects were rhinitis (120 of 601 subjects [20%]), upper respiratory tract infection (16%), diarrhea (12%), irritability (11%), eczema (11%), cough (9%), and pyrexia (8%). No clinically significant differences were noted between two-dose and three-dose MenACWY vaccine groups in the UK or in Canada or among MenACWY and Menjugate vaccine groups.

Forty-eight of 601 subjects (8%) experienced at least one AE that was severe in intensity during the study. There were no major differences in the incidence of severe AEs among the vaccine groups (range = 4% to 11% per group). The most frequently reported severe AEs were bronchiolitis (8 of 601 subjects = 1%) and other infection-related AEs (e.g., upper respiratory tract infection, bronchial hyperreactivity, and pyrexia (< 1% each)). All but one severe AE were considered not related to study vaccine by the investigator; one instance of supraventricular tachycardia was considered possibly related to study vaccine.

No deaths were reported during the study.

Seventy-three subjects experienced SAEs, representing between 4% and 22% of the subjects in the seven vaccine groups. The differences in SAE incidence among the vaccine groups revealed no clinically meaningful patterns. The most frequently reported individual SAEs were bronchiolitis (15 subjects [2%]) and viral infection (8 subjects [1%]). All but two SAEs were considered unrelated to vaccination: one subject in the UK234+ group experienced idiopathic thrombocytopenic purpura, and one subject UK24+ group experienced supraventricular tachycardia. Both events were considered possibly related to study vaccine; both subjects recovered.

Five subjects were prematurely withdrawn from the study due to AEs. All five these subjects were from the UK. Of these, three AEs were considered possibly or probably related, including idiopathic thrombocytopenic purpura, supraventricular tachycardia, and local reaction in the right leg after the third MenACWY vaccination.

Sixteen subjects experienced AEs that lead to an interruption or delay in study vaccination; the most frequently reported of these events was bronchiolitis. Of these, 11 subjects were from the UK, and 5 were from Canada. Three of the 16 AEs were considered possibly or probably related to study vaccine, including rash generalized, supraventricular tachycardia, and local reaction.

All SAEs and significant AEs leading to withdrawal of the subject from the study resolved by the end of

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the study, except for the SAE febrile convulsions, which persisted. No clinically significant differences were observed among the vaccine groups with regard to the incidence or severity of treatment-emergent AEs.

Conclusions

The primary objective of the study was met, supporting the conclusion that three-dose MenACWY Ad+ regimens were highly immunogenic against all four serogroups in UK and Canadian subjects.

Two-dose MenACWY Ad+ and Ad- vaccines were immunogenic against all four serogroups, and there were no significant differences between UK Ad+ and Ad- groups or between Canadian Ad+ and Ad- groups. Immunogenicity was substantially less against the A serogroup than against C, W, and Y serogroups.

A booster dose of MenACWY(Ad+/Ad-) increased the percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 in UK two-dose MenACWY Ad+ and Ad- vaccine groups in the UK and the three-dose MenACWY Ad+ group in the UK. Bactericidal antibody levels were high against all four serogroups at 1 month after the booster dose.

Persistence of the immune response at 12 months of age was similar for the two-dose MenACWY vaccine groups against all four serogroups. There were no differences between adjuvanted and nonadjuvanted formulations. As expected Menjugate subjects in the UK had high levels of antibodies against the C serogroup but very low levels against A, W, and Y serogroups.

Persistence of the immune response at 12 months of age in both UK and Canadian Ad+ vaccine groups was lower against the A serogroup than against the C, W, and Y serogroups.

Reduced-dose polysaccharide challenge at 12 months of age resulted in high percentage of subjects achieving threshold bactericidal antibody levels at 1 month after challenge of Canadian subjects who previously received three doses of MenACWY Ad+ at 2, 4, and 6 months of age (range 89% to 98% of subjects with hSBA ≥ 1:4 among serogroups A, C, W, and Y), and after two doses of MenACWY Ad+ at 2 and 4 months of age (78%, 95%, 98%, and 98%). There were no apparent differences between the three-dose and two-dose regimens against any of the four serogroups.

Similarly, the reduced-dose polysaccharide challenge dose resulted in high percentage of subjects achieving threshold bactericidal antibody levels at 1 month after challenge of Canadian subjects who previously received two doses of MenACWY Ad+ or MenACWY Ad- at 2 and 4 months of age. hSBA GMTs also significantly increased for all serogroups but were lower against the A serogroup than against C, W, and Y serogroups. There were no statistically significant differences in induction of memory response between Ad+ and Ad- groups.

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Persistence (percentages of subjects with hSBA ≥ 1:4, 1:8, and GMTs) was generally higher when three doses of MenACWY Ad+ were given to UK subjects than when two doses were given. Results for Canadian three-dose vs. two-dose comparisons were similar (i.e., three doses were better than two doses).

Routine concomitant vaccines were shown to elicit expected immune responses when given concomitantly with MenACWY Ad+ and Ad- vaccines in both the UK and Canada.

The percentage of subjects with hSBA ≥ 1:4 against serogroup C was significantly higher (98%) at 1 month after primary vaccination in the UK Menjugate group (containing 10 µg of MenC oligosaccharide) than that observed in both of the UK two-dose groups (Ad+, 84%; $P < .007$ for all serogroups; Ad-, 86%, $P = .013$) (each containing 5 µg of MenC oligosaccharide).

All formulations and schedules of Novartis MenACWY vaccine, with or without adjuvant, were safe and well tolerated. There were no noteworthy differences between the groups in the incidence or severity of any AE.

Table 2.1-1 Time and Events: UK Schedule

Group	Visit No.					
	1	2	3	4	5	6
Age	**2 months**	**3 months**	**4 months**	**5 months**	**12 months***	**13 months ***
I	Serology MenACWY Ad + DTaPHibIPV	MenACWY Ad + DTaPHibIPV	MenACWY Ad + DTaPHibIPV	Serology	Serology MenACWY Ad + 	Serology
II	Serology MenACWY Ad + DTaPHibIPV	DTaPHibIPV	MenACWY Ad + DTaPHibIPV	Serology	Serology MenACWY Ad + 	Serology
III	Serology Menjugate DTaPHibIPV	DTaPHibIPV	Menjugate DTaPHibIPV	Serology	Serology MenACWY Ad + 	Serology
VI	Serology MenACWY Ad- DTaPHibIPV	DTaPHibIPV	MenACWY Ad- DTaPHibIPV	Serology	Serology MenACWY Ad- 	Serology

* Due to the +56 day window, visit 5 and visit 6 could occur up to 14 months (visit 5) and 15 months (visit 6) of age.

Table 2.1-2 Time and Events: Canada Schedule

Group	Visit No.					
	1	**2**	**3**	**4**	**5**	**6**
Age	**2 months**	**4 months**	**6 months**	**7 months**	**12 months***	**13 months ***
IV	Serology MenACWY Ad + DTaPHibIPV HBV 7-PnC	MenACWY Ad + DTaPHibIPV HBV 7-PnC	MenACWY Ad + DTaPHibIPV HBV 7-PnC[2]	Serology	Serology Men PS[1] MMR 7-PnC[2]	Serology
Age	**2 months**	**4 months**	**5 months**	**6 months**	**12 months***	**13 months ***
V	Serology MenACWY Ad + DTaPHibIPV HBV 7-PnC	MenACWY Ad + DTaPHibIPV HBV 7-PnC	Serology	DTaPHibIPV HBV 7-PnC	Serology Men PS, or MenACWY Ad + MMR 7-PnC	Serology
VII	Serology MenACWY Ad + DTaPHibIPV HBV 7-PnC	MenACWY Ad + DTaPHibIPV HBV 7-PnC	Serology	DTaPHibIPV HBV 7-PnC[2]	Serology MenACWY Ad + MMR 7-PnC[2]	Serology

Men PS[1] = in a subgroup
Heptavalent pneumococcal conjugate vaccine (7-PnC)[2] = if available

Table 2.1-3 Percentage of Subjects With hSBA Titers ≥ 1:4 Against Serogroups A, C, W, and Y Following Three Doses of MenACWY Ad+ Vaccine

Serogroup	Time of sampling	Parameter	Group I (UK) 2, 3, and 4 months	Group IV (Canada) 2, 4, and 6 months
A	Baseline	% ≥ 1:4 (95% CI) N	6 (2-14) 69	0 (0-5) 80
	1 month after primary	% ≥ 1:4 (95% CI) N	93 (84-98) 69	81 (71-89) 80
C	Baseline	% ≥ 1:4 (95% CI) N	18 (10-28) 79	15 (8-24) 86
	1 month after primary	% ≥ 1:4 (95% CI) N	96 (89-99) 79	98 (92-100) 86
W	Baseline	% ≥ 1:4 (95% CI) N	54 (41-66) 69	31 (21-42) 78
	1 month after primary	% ≥ 1:4 (95% CI) N	97 (90-100) 69	99 (93-100) 78
Y	Baseline	% ≥ 1:4 (95% CI) N	21 (13-31) 81	17 (10-27) 87
	1 month after primary	% ≥ 1:4 (95% CI) N	94 (86-98) 81	98 (92-100) 87

Source: Table 14.2.1.1

Table 2.1-4 Percentage of Subjects With hSBA Titers ≥ 1:8 and hSBA Geometric Mean Titers Following Three Doses of MenACWY Ad+ Vaccine

Serogroup	Time of sampling	Parameter	Group I (UK) MenACWY Ad+ 2, 3, and 4 months		Group IV (Canada) MenACWY Ad+ 2, 4, and 6 months	
			1:8 (%)	GMT/GMR	1:8 (%)	GMT/GMR
A	Baseline	Value (95% CI) N	4 (1-12) 69	2.2 (2.04-2.38) 69	0 (0-5) 80	2 (1.86-2.15) 80
	1 month after primary	Value (95% CI) N	88 (78-95) 69	53 (38-74) 69	76 (65-85) 80	21 (15-29) 80
	1 month after primary	GMR Value (95% CI) N	not applicable	24 (17-34) 69	not applicable	11 (7.62-15) 80
C	Baseline	Value (95% CI) N	9 (4-17) 79	2.79 (2.36-3.31) 79	5 (1-11) 86	2.64 (2.25-3.11) 86
	1 month after primary	Value (95% CI) N	92 (84-97) 79	79 (56-112) 79	98 (92-100) 86	124 (89-172) 86
	1 month after primary	GMR Value (95% CI) N	not applicable	28 (19-43) 79	not applicable	47 (31-70) 86
W	Baseline	Value (95% CI) N	46 (34-59) 69	5.76 (4.39-7.57) 69	28 (19-40) 78	4.03 (3.12-5.21) 78
	1 month after primary	Value (95% CI) N	88 (78-95) 69	65 (46-92) 69	96 (89-99) 78	73 (53-102) 78
	1 month after primary	GMR Value (95% CI) N	not applicable	11 (7.29-18) 69	not applicable	18 (12-28) 78
Y	Baseline	Value (95% CI) N	14 (7-23) 81	2.72 (2.34-3.17) 81	11 (6-20) 87	2.64 (2.28-3.05) 87
	1 month after primary	Value (95% CI) N	93 (85-97) 81	56 (41-77) 81	89 (80-94) 87	64 (47-87) 87
	1 month after primary	GMR Value (95% CI) N	not applicable	21 (14-30) 81	not applicable	24 (17-34) 87

Source: Tables 14.2.1.5 and 14.2.1.9

Table 2.1-5 Percentage of Subjects With hSBA Titers ≥ 1:8 and hSBA Geometric Mean Titers Following Two Doses of MenACWY Ad+ Vaccine

Sero-group	Time of sampling	Parameter	Group II (UK) (MenACWY Ad+ at 2 and 4 months)			Group V (Canada) (MenACWY Ad+ at 2 and 4 months)			Group VI (UK) (MenACWY Ad- at 2 and 4 months)			Group VII (Canada) (MenACWY Ad- at 2 and 4 months)		
			1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR
A	Baseline	Value (95% CI) N	4 (1-12) 68	3 (0-10) 68	2.17 (1.96-2.4) 68	3 (0-9) 79	1 (0.032-7) 79	2.07 (1.99-2.15) 79	3 (0-9) 78	0 (0-5) 78	2.05 (1.87-2.26) 78	4 (1-10) 83	1 (0.03-7) 83	2.08 (2-2.16) 83
	1 month after primary	Value (95% CI) N	60 (48-72) 68	54 (42-67) 68	12 [a] (8.36-16) 68	66 (54-76) 79	58 (47-69) 79	11 (7.71-14) 79	50 (38-62) 78	44 (32-55) 78	7.3 [a] (5.31-10) 78	57 (45-67) 83	49 (38-61) 83	7.2 (5.26-9.79) 83
		GMR (95% CI)			5.41 (3.81-7.74)			5.11 (3.72-7.02)			3.56 (2.55-4.97)			3.46 (2.54-4.72)
C	Baseline	Value (95% CI) N	13 (6-23) 77	9 (4-18) 77	2.54 (2.18-2.96) 77	15 (8-25) 74	15 (8-25) 74	2.88 (2.36-3.51) 74	20 (12-31) 79	5 (1-12) 79	2.48 (2.13-2.88) 79	20 (12-30) 85	11 (5-19) 85	2.87 (2.39-3.44) 85
	1 month after primary	Value (95% CI) N	84 (74-92) 77	83 (73-91) 77	52 (36-75) 77	91 (81-96) 74	85 (75-92) 74	53 (37-75) 74	86 (76-93) 79	82 (72-90) 79	40 (28-57) 79	93 (85-97) 85	89 (81-95) 85	69 (50-95) 85
		GMR (95% CI)			20 (13-31)			18 (12-29)			16 (11-24)			24 (16-36)
W	Baseline	Value (95% CI) N	45 (34-57) 73	37 (26-49) 73	5.33 (4.04-7.03) 73	24 (15-36) 74	19 (11-30) 74	3.68 (2.86-4.74) 74	43 (31-55) 72	36 (25-48) 72	5.14 (3.89-6.79) 72	19 (11-29) 75	16 (9-26) 75	3.02 (2.34-3.86 75
	1 month after primary	Value (95% CI) N	92 (83-97) 73	84 (73-91) 73	48 [b] (34-68) 73	91 (81-96) 74	85 (75-92) 74	42 [c] (31-58) 74	82 (71-90) 72	75 (63-84) 72	29 [b] (20-41) 72	95 (87-99) 75	92 (83-97) 75	70 [c] (51-96) 75
		GMR (95% CI)			9 (5.74-14)			12 [d] (7.69-17)			5.55 (3.531-8.74)			23 [d] (16-35)
Y	Baseline	Value (95% CI) N	18 [f] (10-29) 76	7 (2-15) 76	2.56 (2.17-3.02) 76	9 (4-19) 74	4 [g] (1-11) 74	2.29 (1.97-2.66) 74	35 [f] (25-47) 77	16 (8-26) 77	3.39 (2.87-4) 77	18 (10-27) 85	11 [g] (5-19) 85	2.76 (2.4-3.17) 85

Sero-group	Time of sampling	Parameter	Group II (UK) (MenACWY Ad+ at 2 and 4 months)			Group V (Canada) (MenACWY Ad+ at 2 and 4 months)			Group VI (UK) (MenACWY Ad- at 2 and 4 months)			Group VII (Canada) (MenACWY Ad- at 2 and 4 months)		
			1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR	1:4 (%)	1:8 (%)	GMT /GMR
	1 month after primary	Value (95% CI) N	84 (74-92) 76	76 (65-85) 76	26 (19-37) 76	86 (77-93) 74	80 (69-88) 74	26 [e] (19-36) 74	74 (63-83) 77	70 (59-80) 77	21 (15-29) 77	91 (82-96) 85	86 (77-92) 85	41 [e] (30-55[22]) 85
		GMR (95% CI)			10 (7.06-15)			11 (7.79-16)			6.14 (4.22-8.93)			15 (11-21)
Source Table			14.2.1.1	14.2.1.5	14.2.1.9	14.2.1.1	14.2.1.5	14.2.1.9	14.2.1.1	14.2.1.5	14.2.1.9	14.2.1.1	14.2.1.5	14.2.1.9

Table 2.1-6 Percentage of UK Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and GMTs and GMRs, After a Booster Dose of MenACWY Ad+ or Ad- Vaccine Following Two or Three Doses of MenACWY Ad+ or Ad- Vaccine

Serogroup	Time of sampling		Group II (UK) [UK24+ACWY] (MenACWY Ad+ at 2 and 4 months)				Group VI (UK) [UK24-ACWY] (MenACWY Ad- at 2 and 4 months)				Group I (UK) [UK234+] (MenACWY Ad+ at 2, 3, and 4 months)			
			1:4 (%)	1:8 (%)	GMT	GMRs	1:4 (%)	1:8 (%)	GMT	GMRs	1:4 (%)	1:8 (%)	GMT	GMRs
A	At 12 months	Value (95% CI) N	8 (3-17) 64	5 (1-13) 64	2.31 (2-2.66) 64		7 (2-16) 61	5 (1-14) 61	2.22 (1.92-2.57) 61		21 (12-33) 62	13 (6-24) 62	2.97 (2.57-3.44) 62	
	1 month after booster	Value (95% CI) N	86 (75-93) 64	83 (71-91) 39	47 (31-72) 64	20 (14-30)	79 (66-88) 61	77 (65-87) 61	30 (19-47) 61	14 (9.01-20)	94 (84-98) 62	92 (82-97) 62	134 (87-207) 62	45 (30-68)
C	At 12 months	Value (95% CI) N	40 (28-53) 67	34 (23-47) 67	5.18 (3.83-7.02) 67		33 (22-46) 63	27 (17-40) 63	3.94 (2.88-5.39) 63		60 (47-72) 65	52 (40-65) 65	7.94 (5.84-11) 65	
	1 month after booster	Value (95% CI) N	96 (87-99) 57	96 (87-99) 67	236 (159-349) 67	45 (33-62)	94 (85-98) 40	94 (85-98) 63	129 (86-194) 63	33 (24-45)	98 (92-100) 65	98 (92-100) 65	429 (288-639) 65	54 (40-74)
W	At 12 months	Value (95% CI) N	56 (42-69) 57	47 (34-61) 57	8.1 (5.76-11) 57		54 (37-69) 41	41 (26-58) 41	6.49 (4.34-9.7) 41		81 (68-90) 57	68 (55-80) 57	16 (11-23) 57	
	1 month after booster	Value (95% CI) N	100 (94-100) 57	100 (94-100) 57	503 (347-732) 57	62 (45-85)	100 (91-100) 41	100 (91-100) 41	311 (200-485) 41	48 (33-70)	100 (94-100) 40	100 (94-100) 57	792 (544-1154) 57	49 (36-68)
Y	At 12 months	Value (95% CI) N	52 (39-64) 66	39 (28-52) 66	6.65 (4.88-9.06) 66		52 (39-65) 63	41 (29-54) 63	6.83 (4.98-9.37) 63		86 (75-93) 65	72 (60-83) 65	19 (14-26) 65	
	1 month after booster	Value (95% CI) N	100 (95-100) 66	100 (95-100) 66	508 (358-723) 66	76 (56-104)	100 (94-100) 63	100 (94-100) 63	438 (305-628) 63	64 (47-88)	100 (94-100) 65	100 (94-100) 65	1395 (979-1989) 65	74 (55-101)

Source: Tables 14.2.1.3, 14.2.1.7 and 14.2.1.11. [Brackets = SAS code for vaccine groups in source tables] For group I, values at 12 months are the subgroup that did not receive the booster dose. For group II, values at 12 months are the subgroup that received MenACWY Ad+ booster dose. For group VI, values at 12 months are the subgroup that received MenACWY Ad- booster dose. These subgroups did not receive the reduced-dose PS challenge.
GMT and GMR values are least-square means from the ANOVAs of log-transformed geometric mean titers.

Table 2.1-7 Percentage of Canadian Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and GMTs and GMRs, After a Booster Dose of MenACWY Ad+ or Ad- Vaccine Following Two Doses of MenACWY Ad+ or Ad- Vaccine

Serogroup	Time of sampling		Group V (Canada) [CA24+ACWY] (MenACWY Ad+ at 2 and 4 months)				Group VII (Canada) [CA24-ACWY] (MenACWY Ad- at 2 and 4 months)			
			1:4 (%)	1:8 (%)	GMT	GMRs	1:4 (%)	1:8 (%)	GMT	GMRs
A	At 12 months	Value (95% CI) N	5 (1-17) 39	3 (0.065-13) 39	2.18 (1.74-2.73) 39		3 (0.067-14) 38	3 (0.067-14) 38	2.07 (1.65-2.6) 38	
	1 month after booster	Value (95% CI) N	92 (79-98) 39	90 (76-97) 39	67 (43-106) 39	31 (21-47)	95 (82-99) 38	92 (79-98) 38	59 (38-93) 38	29 (19-43)
C	At 12 months	Value (95% CI) N	48 (32-64) 40	35 (21-52) 40	4.64 (3.11-6.91) 40		33 (19-49) 40	25 (13-41) 40	4.07 (2.73-6.06) 40	
	1 month after booster	Value (95% CI) N	98 (87-100) 40	95 (83-99) 40	216 (130-356) 40	46 (31-69)	100 (91-100) 40	100 (91-100) 40	258 (156-426) 40	63 (43-94)
W	At 12 months	Value (95% CI) N	74 (57-88) 35	49 (31-66) 35	8.84 (5.63-14) 35		69 (51-83) 35	54 (37-71) 35	11 (7.04-17) 35	
	1 month after booster	Value (95% CI) N	100 (90-100) 35	100 (90-100) 35	381 (224-650) 35	43 (29-65)	100 (90-100) 35	100 (90-100) 35	402 (236-684) 35	36 (24-55)
Y	At 12 months	Value (95% CI) N	65 (48-79) 40	45 (29-62) 40	7.99 (5.29-12) 40		63 (46-78) 38	53 (36-69) 38	7.63 (5-12) 38	
	1 month after booster	Value (95% CI) N	100 (91-100) 40	100 (91-100) 40	308 (191-499) 40	39 (27-56)	100 (91-100) 38	100 (91-100) 38	527 (322-862) 38	69 (47-101)

Source: Tables 14.2.1.4, 14.2.1.8 and 14.2.1.12. [Brackets = SAS code for vaccine groups in source tables] For group V, values at 12 months are the subgroup that received MenACWY Ad+ booster dose. For group VII, values at 12 months are the subgroup that received MenACWY Ad- booster dose. These subgroups did not receive the reduced-dose PS challenge.
GMT and GMR values are least-square means from the ANOVAs of log-transformed geometric mean titers.

Table 2.1-8 Percentages of Canadian Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and hSBA GMTs, Following Two Doses of MenACWY Ad+ Vaccine or Two Doses of MenACWY Ad- Vaccine

Serogroup	Time of sampling (age in months)	Parameter	Group V (Canada) (MenACWY Ad+ at 2 and 4 months)			Group VII (Canada) (MenACWY Ad- at 2 and 4 months)		
			1:4 (%)	1:8 (%)	GMT	1:4 (%)	1:8 (%)	GMT
A	5 months	Value (95% CI) N	65 (53-75) 77	57 (45-68) 77	11 (7.72-15) 77	56 (45-66) 78	50 (38-62) 78	6.91 (5.03-9.49) 78
	At 12 months	Value (95% CI) N	8 (3-16) 77	5 (1-13) 77	2.29 (1.98-2.65) 77	5 (1-13) 78	4 (1-11) 78	2.18 (1.89-2.52) 78
C	5 months	Value (95% CI) N	92 (83-97) 73	86 (76-93) 73	58 (40-8224) 73	93 (85-97) 81	89 (80-95) 81	65 (46-92) 81
	At 12 months	Value (95% CI) N	48 (36-60) 73	40 (28-52) 73	5.43 (4.05-7.27) 73	35 (24-46) 81	30 (20-41) 81	4.42 (3.35-5.84) 81
W	5 months	Value (95% CI) N	90 (80-96) 69	84 (73-92) 69	41 (29-58) 69	94 (86-98) 69	91 (82-97) 69	67 (47-94) 69
	At 12 months	Value (95% CI) N	64 (51-75) 69	52 (40-64) 69	8.15 (5.97-11) 69	75 (64-85) 69	61 (48-72) 69	12 (8.81-16) 69
Y	5 months	Value (95% CI) N	86 (76-93) 73	79 (68-88) 73	27 (19-38) 73	91 (83-96) 79	86 (76-93) 79	39 (28-54) 79
	At 12 months	Value (95% CI) N	60 (48-72) 73	51 (39-63) 73	7.84 (5.79-11) 73	59 (48-70) 79	46 (34-57) 79	7.12 (5.32-9.54) 79

Source: Tables 14.2.1.2, 14.2.1.6, and 14.2.1.10. For group V, the values at 12 months of age are of the subgroup that received the MenACWY Ad+ booster dose. For group VII, the values at 12 months of age are of the subgroup that received the MenACWY Ad- booster dose. These subgroups did not receive the reduced-dose PS challenge.

Table 2.1-9 Percentages of Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and hSBA GMTs, Following Three Doses of MenACWY Ad+ Vaccine

Serogroup	Time of sampling (age in months)		Group I (UK) (MenACWY Ad+ at 2, 3, and 4 months)			Group IV (Canada) (MenACWY Ad+ at 2, 4, and 6 months)		
			1:4 (%)	1:8 (%)	GMT	1:4 (%)	1:8 (%)	GMT
A	1 month after primary	Value (95% CI) N	91 (81-97) 58	86 (75-94) 58	55 (38-80) 58	82 (72-90) 79	77 (66-86) 79	22 (16-30) 79
	At 12 months	Value (95% CI) N	21 (11-33) 58	16 (7-27) 58	3.02 (2.55-3.57) 58	35 (25-47) 79	29 (19-40) 79	3.93 (3.4-4.54) 79
C	1 month after primary	Value (95% CI) N	96 (88-99) 70	91 (82-97) 70	79 (55-114) 70	98 (92-100) 84	98 (92-100) 84	123 (88-172) 84
	At 12 months	Value (95% CI) N	59 (46-70) 70	47 (35-59) 70	7.56 (5.61-10) 70	75 (64-84) 84	68 (57-78) 84	14 (10-18) 84
W	1 month after primary	Value (95% CI) N	97 (88-100) 58	86 (75-94) 58	62 (43-90) 58	99 (93-100) 75	96 (89-99) 75	74 (53-103) 75
	At 12 months	Value (95% CI) N	78 (65-87) 58	66 (52-78) 58	15 (10-21) 58	89 (80-95) 75	81 (71-89) 75	20 (15-27) 75
Y	At 5 or 7 months	Value (95% CI) N	93 (84-98) 71	92 (83-97) 71	55 (39-78) 71	98 (92-100) 86	88 (80-94) 86	65 (47-88) 86
	1 month after primary	Value (95% CI) N	85 (74-92) 71	70 (58-81) 71	18 (13-24) 71	87 (78-93) 86	79 (69-87) 86	22 (17-29) 86

Source: Tables 14.2.1.2, 14.2.1.6, and 14.2.1.10.

Table 2.1-10 Percentages of Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and hSBA GMTs, in Subjects Challenged With a Reduced Dose of Licensed Meningococcal PS Vaccine Following Three Doses of MenACWY Ad+ Vaccine (Group IV)

Serogroup	Time of sampling	Parameter	Group IV (Canada) (MenACWY Ad+ at 2, 4, and 6 months)		
			1:4 (%)	1:8 (%)	GMT
A	Before challenge at 12 months	Value (95% CI) N	27 (15-43) 44	23 (11-38) 44	3.4 (2.75-4.2) 44
	1 month after PS challenge	Value (95% CI) N	89 (75-96) 44	86 (73-95) 44	32 (21-48) 44
C	Before challenge at 12 months	Value (95% CI) N	74 (59-86) 43	65 (49-79) 43	12 (8.41-18) 43
	1 month after PS challenge	Value (95% CI) N	95 (84-99) 43	91 (78-97) 43	82 (50-133) 43
W	Before challenge at 12 months	Value (95% CI) N	83 (67-93) 40	73 (56-85) 40	17 (11-25) 40
	1 month after PS challenge	Value (95% CI) N	98 (87-100) 40	95 (83-99) 40	249 (152-410) 40
Y	Before challenge at 12 months	Value (95% CI) N	89 (75-96) 44	77 (62-89) 44	19 (13-28) 44
	1 month after PS challenge	Value (95% CI) N	98 (88-100) 44	98 (88-100) 44	186 (117-294) 44

Source: Tables 14.2.1.4, 14.2.1.8 and 14.2.1.12

Table 2.1-11 Percentage of Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8, and hSBA GMTs, in Subjects Challenged With a Reduced Dose of a Licensed Meningococcal PS Vaccine Following Two Doses of MenACWY Ad+ or Ad- Vaccine (Groups V and VII)

Serogroup	Time of sampling	Parameter	Group V (Canada) (MenACWY Ad+ at 2 and 4 months)			Group VII (Canada) (MenACWY Ad- at 2 and 4 months)		
			1:4 (%)	1:8 (%)	GMT	1:4 (%)	1:8 (%)	GMT
A	Before challenge at 12 months	Value (95% CI) N	8 (2-20) 40	5 (1-17) 40	2.22 (1.77-2.76) 40	8 (2-21) 39	5 (1-17) 39	2.31 (1.84-2.89) 39
	1 month after PS challenge	Value (95% CI) N	78 (62-89) 40	78 (62-89) 40	28 (18-44) 40	92 (79-98) 39	87 (73-96) 39	55 (35-86) 39
C	Before challenge at 12 months	Value (95% CI) N	44 (28-60) 41	39 (24-55) 41	5.21 (3.51-7.72) 41	38 (23-55) 39	36 (21-53) 39	5.07 (3.38-7.59) 39
	1 month after PS challenge	Value (95% CI) N	95 (83-99) 41	93 (80-98) 41	140 (85-231) 41	95 (83-99) 39	90 (76-97) 39	181 (109-301) 39
W	Before challenge at 12 months	Value (95% CI) N	59 (42-74) 41	51 (35-67) 41	7.48 (4.94-11) 41	71 (54-85) 38	58 (41-74) 38	11 (7.08-17) 38
	1 month after PS challenge	Value (95% CI) N	98 (87-100) 41	98 (87-100) 41	365 (224-597) 41	100 (91-100) 38	100 (91-100) 38	555 (333-924) 38
Y	Before challenge at 12 months	Value (95% CI) N	55 (39-70) 42	50 (34-66) 42	6.73 (4.51-10) 42	55 (38-71) 38	42 (26-59) 38	6.79 (4.45-10) 38
	1 month after PS challenge	Value (95% CI) N	98 (87-100) 42	98 (87-100) 42	280 (175-448) 42	100 (91-100) 38	97 (86-100) 38	288 (176-472) 38

Source: Tables 14.2.1.4, 14.2.1.8, and 14.2.1.12.

Table 2.1-12 **Percentage of Subjects With hSBA Titers ≥ 1:4 and ≥ 1:8 Following Two or Three Doses of MenACWY Ad+ Vaccine**

Serogroup	Time of sampling	Parameter	Group I (UK) (MenACWY Ad+) (2, 3, and 4 months)		Group IV (Canada) (MenACWY Ad+) (2, 4, and 6 months)		Group II (UK) (MenACWY Ad+) (2 and 4 months)		Group V (Canada) (MenACWY Ad+) (2 and 4 months)	
			1:4 (%)	1:8 (%)	1:4 (%)	1:8 (%)	1:4 (%)	1:8 (%)	1:4 (%)	1:8 (%)
A	Baseline	Value (95% CI) N	6 (2-14) 69	4 (1-12) 69	0 (0-5) 80	0 (0-5) 80	4 (1-12) 68	3 (0-10) 68	3 (0-9) 79	1 (0.032-7) 79
	1 month after primary	Value (95% CI) N	93 (84-98) 69	88 (78-95) 69	81 (71-89) 80	76 (65-85) 80	60 (48-72) 68	54 (42-67) 68	66 (54-76) 79	58 (47-69) 79
C	Baseline	Value (95% CI) N	18 (10-28) 79	9 (4-17) 79	15 (8-24) 86	5 (1-11) 86	13 (6-23) 77	9 (4-18) 77	15 (8-25) 74	15 (8-25) 74
	1 month after primary	Value (95% CI) N	96 (89-99) 79	92 (84-97) 79	98 (92-100) 86	98 (92-100) 86	84 (74-92) 77	83 (73-91) 77	91 (81-96) 74	85 (75-92) 74
W	Baseline	Value (95% CI) N	54 (41-66) 69	46 (34-59) 69	31 (21-42) 78	28 (19-40) 78	45 (34-57) 73	37 (26-49) 73	24 (15-36) 74	19 (11-30) 74
	1 month after primary	Value (95% CI) N	97 (90-100) 69	88 (78-95) 69	99 (93-100) 78	96 (89-99) 78	92 (83-97) 73	84 (73-91) 73	91 (81-96) 74	85 (75-92) 74
Y	Baseline	Value (95% CI) N	21 (13-31) 81	14 (7-23) 81	17 (10-27) 87	11 (6-20) 87	18 (10-29) 76	7 (2-15) 76	9 (4-19) 74	4 (1-11) 74
	1 month after primary	Value (95% CI) N	94 (86-98) 81	93 (85-97) 81	98 (92-100) 87	89 (80-94) 87	84 (74-92) 76	76 (75-85) 76	86 (77-93) 74	80 (69-88) 74

Source: Tables 14.2.1.1, 14.2.1.1.1, 14.2.1.1.2, 14.2.1.5, 14.2.1.5.1 and 14.2.1.5.2.

Table 2.1-13 Percentage of Subjects With hSBA Titers ≥ 1:4 or ≥ 1:8 in Subjects Challenged With a Reduced Dose of a Licensed Meningococcal PS Vaccine Following Two or Three Doses of MenACWY Ad+ Vaccine (Groups IV and V)

Serogroup	Time of sampling	Parameter	Group IV (Canada) (MenACWY Ad+) (2, 4, and 6 months)		Group V (Canada) (MenACWY Ad+) (2 and 4 months)	
			1:4 (%)	1:8 (%)	1:4 (%)	1:8 (%)
A	At 12 months	Value (95% CI) N	27 (15-43) 44	23 (11-38) 44	8 (2-20) 40	5 (1-17) 40
	1 month after PS challenge	Value (95% CI) N	89 (75-96) 44	86 (73-95) 44	78 (62-89) 40	78 (62-89) 40
C	At 12 months	Value (95% CI) N	74 (59-86) 43	65 (49-79) 43	44 (28-60) 41	39 (24-55) 41
	1 month after PS challenge	Value (95% CI) N	95 (84-99) 43	91 (78-97) 43	95 (83-99) 41	93 (80-98) 41
W	At 12 months	Value (95% CI) N	83 (67-93) 40	73 (56-85) 40	59 (42-74) 41	51 (35-67) 41
	1 month after PS challenge	Value (95% CI) N	98 (87-100) 40	95 (83-99) 40	98 (87-100) 41	98 (87-100) 41
Y	At 12 months	Value (95% CI) N	89 (75-96) 44	77 (62-89) 44	55 (39-70) 42	50 (34-66) 42
	1 month after PS challenge	Value (95% CI) N	98 (88-100) 44	98 (88-100) 44	98 (87-100) 42	98 (87-100) 42

Source: Tables 14.2.1.4 and 14.2.1.8

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics, Inc. 4560 Horton Street Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P6**	

Title of Study: A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine With or Without Aluminum Phosphate Adjuvant With the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

Protocol Number: V59P6

Investigators: Lisa A. Jackson, MD, MPH, Group Health Cooperative, Center for Health Studies, Seattle, Washington; Keith S. Reisinger, MD, MPH, Primary Physicians Research, Inc., Pittsburgh, Pennsylvania; Robert M. Jacobson, MD, Mayo Vaccine Research Group, Rochester, Minnesota.

Study Centers: Seattle, Washington; Pittsburgh, Pennsylvania; Rochester, Minnesota.

Publication (reference): None.

Study Period: (date of first enrolment) 29 OCT 04 (date of last completed) 31 MAR 06	**Phase of Development:** Phase 2

Objectives:

Immunogenicity Objectives

Primary Objectives

1. To compare the immunogenicity of a single dose of either the adjuvanted (MenACWY+) or unadjuvanted (MenACWY-) formulation of MenACWY conjugate vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to adolescents 11 to 17 years of age.

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P6**	

- Group 1 (MenACWY conjugate vaccine with Aluminum Phosphate Adjuvant, MenACWY+) vs. Group 2 (Menomune®)
- Group 3 (MenACWY conjugate vaccine without Aluminum Phosphate Adjuvant, MenACWY-) vs. Group 2 (Menomune®)

Secondary Objectives

1. To compare the immunogenicity of a single dose of either the MenACWY+ or MenACWY- vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as SBA geometric mean titer [GMT] antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to adolescents 11 to 17 years of age.
2. To evaluate the immunogenicity of a single dose of either the MenACWY+ or MenACWY- formulation of MenACWY conjugate vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as percentage of subjects with hSBA ≥ 1:4 directed against *N meningitidis* serogroups A, C, W-135, and Y, at 12 months after vaccination, when administered to adolescents 11 to 17 years of age.
3. To evaluate the immunogenicity of a single dose of either the MenACWY+ or MenACWY- formulation of MenACWY conjugate vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as SBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at 12 months after vaccination, when administered to adolescents 11 to 17 years of age.
4. Exploratory analyses of the quantity and quality of memory B-cells in the peripheral blood in a subset of subjects at 12 months after vaccination using a meningococcal capsule-specific B-cell ELISPOT assay.

Safety Objectives

To assess the safety and tolerability of a single dose of either the MenACWY+ or MenACWY- formulation of MenACWY conjugate vaccine compared to the safety and

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tolerability of a single dose of Menomune® when administered to adolescents 11 to 17 years of age.

Methodology: This trial was a phase 2, randomized, single-blind, controlled, multicenter study to evaluate the safety and immune response at 1 month and 12 months following vaccination with one dose of either MenACWY+ or MenACWY- ACWY conjugate vaccine or Menomune® in healthy adolescents 11 to 17 years of age. According to the original protocol, healthy adolescents were to be enrolled and randomized to MenACWY+ or Menomune vaccination groups. Due to the addition of a third study group after enrollment began, the study was divided into two stages: the first stage randomized subjects to MenACWY+ or Menomune in a 1:1 ratio; the second stage randomized subjects to MenACWY- or Menomune in a 4:1 ratio. Enrollment in stage 2 was to commence after enrollment in stage 1 was completed. Other than the randomization ratio, the methodology of the two stages of the study was identical.

Number of Subjects (planned and analyzed): A total of 490 subjects were to be enrolled according to the protocol, 300 in stage 1 (150 subjects each in MenACWY+ and Menomune groups) and 190 in stage 2 (152 subjects in the MenACWY- group and 38 subjects in the Menomune group). A total of 524 subjects were actually enrolled, 334 in stage 1 and 190 in stage 2. A convenience subset of subjects enrolled at Site 01 (Group Health Cooperative, Seattle, WA) was to be identified for additional study. These subjects were to provide an additional blood sample at 12 months after vaccination so that meningococcal capsule-specific memory B-cells could be studied in this population.

During stage 1, 164 MenACWY+ and 170 Menomune subjects were analyzed for safety, and 162 MenACWY+ and 170 Menomune subjects were analyzed for immunogenicity (modified intent-to-treat [MITT]); during stage 2, 151 MenACWY- and 39 Menomune subjects were analyzed for safety, and 150 MenACWY- and 39 Menomune subjects were analyzed for immunogenicity (MITT).

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

Adolescents (male and female) eligible to be enrolled in the study were those:

1. who were between 11 and 17 years of age inclusive and were available for all visits and telephone calls scheduled for the study;
2. who gave written assent and/or for whom the parent or legal guardian provided written informed consent after the nature of the study was explained;
3. who were in good health as determined by:
   - medical history,
   - physical examination,
   - clinical judgment of the investigator.

Exclusion Criteria

Adolescents not eligible to be enrolled in the study were those:

1. who or whose parents or legal guardians were perceived to be unreliable or unavailable for the duration of the study period;
2. who had a previous suspected disease caused by *N meningitidis*;
3. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* serogroup A, C, W, and/or Y infection within 60 days prior to enrollment;
4. who had previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational);
5. who had received any investigational agents or vaccines 90 days prior to enrollment;
6. who had received any licensed vaccines within the 30 days prior to enrollment or for whom receipt of a licensed vaccine was anticipated within the 30 days after vaccination. (Exception: Influenza vaccine could have been administered 15 days prior to study vaccination and 15 days after study vaccination);
7. who planned to receive the recommended vaccines such as Td/Hepatitis B series, MMR, Varicella, or Hepatitis A series between visit 1 and visit 2. (Recommended vaccines for this age group may be administered after the blood draw at visit 2);
8. with any serious acute illness;

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9. who were pregnant or nursing (breastfeeding) mothers or females of childbearing age who had not used or did not plan to use acceptable birth control measures, as determined by the investigator for the 12-month duration of the study. Abstinence was considered an acceptable form of contraception. (Females were to have a urine pregnancy test sensitive to 20 IU beta human chorionic gonadotropin (b-hCG) at entry);
10. with any serious chronic or progressive disease (e.g., any history of neoplasm, insulin-dependent diabetes, cardiac disease, autoimmune disease, human immunodeficiency virus infection or acquired immunodeficiency syndrome, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: subjects with mild asthma were eligible for enrollment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids were not eligible for enrollment);
11. with epilepsy or any progressive neurological disease;
12. with a history of any anaphylactic shock, pulmonary reactivity, urticaria, or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;
13. with a known or suspected disease of the immune system, or those receiving immunosuppressive therapy, including use of any systemic corticosteroids, or those who had received blood, blood products, or a parenteral immunoglobulin preparation within 60 days prior to study enrollment;
14. who had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (Exception: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.] may be enrolled 7 days after the last dose);
15. known to have a bleeding diathesis, or any condition that may have been associated with a prolonged bleeding time;
16. with Down's syndrome or other known cytogenic disorders;
17. with an oral temperature of 38.0ºC (100.4ºF) or more within 3 days prior to study entry;
18. with any condition that, in the opinion of the investigators, might interfere with the evaluation of the study objectives.

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Test Product, Dose, Mode of Administration, Lot Number:

The investigational MenACWY conjugate vaccine was constituted by extemporaneous mixing of the lyophilized Men A component to be resuspended with the Men CWY liquid component and was to be prepared just prior to administration to the study subject. After reconstitution, MenACWY conjugate vaccine had the following composition per 0.5 mL of injectable suspension:

Composition	**Quantity per 0.5 mL dose**
Cross Reactive Material $(CRM)_{197}$-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Aluminum phosphate†	0.3 mg Al^{3+}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	
Water for Injection	

†Formulation without adjuvant was identical except aluminum phosphate was not present.

The following lot numbers were used in this study: U79P27D1B (formulation with adjuvant); U79P29D1B (formulation without adjuvant).

One 0.5 mL dose of the MenACWY vaccine was injected intramuscularly (IM) in the left deltoid muscle.

Duration of Study: The duration of participation for each subject was approximately 12 months.

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Reference Therapy, Dose, Mode of Administration, Lot Number:

Menomune® (manufactured by Aventis Pasteur Inc., Swiftwater, Pennsylvania) was supplied as a single dose (one vial of vaccine and one vial of diluent). The vaccine consisted of four meningococcal capsular polysaccharide serogroups (A, C, W-135, and Y). After reconstitution with the liquid diluent, Menomune had the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
Isolated product from each of groups A, C, Y, and W-135	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: Water for injection	Qs to 0.5 mL

One 0.5 mL dose of Menomune was administered subcutaneously (SC) in the left upper arm. Two lots of Menomune were used in this trial: UE267AAB and UE155AAA.

Criteria for Evaluation:

Immunogenicity

The ability of MenACWY conjugate vaccine to elicit functional SBA against each serogroup in the presence of human complement (hSBA) was measured. For each serogroup, hSBA was expressed as the GMT and the percentage of subjects with hSBA response $\geq$ 1:4. Additional analyses may have been performed to further describe the bactericidal response (e.g., hSBA % $\geq$ 1:8).

Safety

The measures of safety used in this study consisted of local and systemic reactions, and other adverse events (AEs). The assessment of local reactions included pain, erythema, and induration. The assessment of systemic reactions included chills, nausea, malaise, myalgia, arthralgia, and headache. Safety was described in terms of the number of subjects with reported local and systemic reactions and/or all AEs through day 7 and/or all serious adverse events (SAEs) and/or AEs requiring a physician visit and/or resulting in premature withdrawal from the study, per vaccination group, through study termination.

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Statistical Methods:

The null hypothesis associated with the primary immunogenicity objective was that the proportion of subjects who were responders (i.e., hSBA titer ≥ 1:4) to MenACWY (either adjuvanted or unadjuvanted) at 1 month after vaccination was inferior to the proportion of subjects who were responders to Menomune for the same serogroup. A given MenACWY serogroup was determined to be noninferior to that serogroup of Menomune if the lower limit of the two-sided 95% confidence interval (CI) around the difference in proportions ($P_{MenACWY}$ minus $P_{Menomune}$) was greater than -10%. This was equivalent to a one-sided 97.5% CI.

To facilitate the planning of future trials, a preliminary analysis was planned to assess immunogenicity and 1-month safety (including local and systemic postvaccination reactions within 7 days of immunization) after all subjects completed visit 2. The results of these analyses did not alter the course of the trial. These analyses were governed by the procedures specified in the Novartis Vaccines and Diagnostics, Inc., Biostatistics and Clinical Data Management (BCDM) document entitled "Interim Analysis in a Clinical Trial."

Summary and Conclusions:

Immunogenicity results

The primary endpoint of this trial was reached, as both MenACWY+ and MenACWY- vaccine groups were found to be noninferior to Menomune in the percentages of subjects with hSBA titers ≥ 1:4 for all serogroups. Both MenACWY+ and MenACWY- vaccine groups had significantly higher percentage of subjects with hSBA titers ≥ 1:4 than Menomune against serogroups A, C, and Y at 1 month after vaccination. Similar results were observed for all four serogroups when a more stringent cutoff of hSBA ≥ 1:8 was used in the assay, as both MenACWY+ and MenACWY- vaccine groups were noninferior to Menomune at 1 month after vaccination. MenACWY+ had significantly higher percentage of subjects with hSBA ≥ 1:8 than Menomune for all four serogroups, while the MenACWY- vaccine group had significantly higher percentage of subjects with hSBA ≥ 1:8 for serogroups A, C, and Y and was noninferior to Menomune for serogroup W.

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At 1 month after study vaccination, both MenACWY+ and MenACWY- groups had significantly higher hSBA GMTs than the Menomune group and significantly greater percentages of subjects with at least a 4-fold rise in hSBA titers against serogroups A, C, and Y. For serogroup W, only the MenACWY- group had a significantly greater percentage of subjects with at least a 4-fold rise in hSBA than Menomune. The MenACWY- group also had a significantly greater percentage of subjects with at least a 4-fold rise in hSBA than the MenACWY+ group; MenACWY+ and Menomune groups did not differ.

After discussion with regulatory authorities and after testing was complete for the sera 1 month after vaccination, Novartis Vaccines decided to continue development of the unadjuvanted formulation (MenACWY-) and not the adjuvanted formulation (MenACWY+). At this time, results at 12 months after vaccination are available for the MenACWY- subjects and a comparable number of PS subjects (all PS stage 2 subjects and a random selection of PS stage 1 subjects)

The MenACWY- vaccine group exhibited a significantly greater percentage of subjects with hSBA titers ≥ 1:4 at 12 months after study vaccination than the Menomune group against serogroups C, W, and Y and was comparable with Menomune for serogroup A.

The MenACWY- vaccine group had significantly higher hSBA GMTs than the Menomune group against serogroups W and Y at 12 months after vaccination. Against serogroups A and C, GMTs were not significantly different between MenACWY- and Menomune groups.

Safety results

Overall, 75% to 84% of subjects in all groups experienced at least one local or systemic reaction. The percentages of subjects who experienced any local reactions (60% to 71% among the four groups) and any systemic reactions (44% to 59%) were similar among the groups. Headache and myalgia were the most frequently reported systemic reactions (204 and 90 subjects, respectively), followed by malaise (63 subjects), nausea (57 subjects), chills (52 subjects), arthralgia (32 subjects), and fever ≥ 38°C (7 subjects). The incidence of systemic reactions was similar among the four vaccine groups.

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Few systemic reactions were severe in intensity. The incidence of severe systemic reactions did not exceed 1% of subjects in the MenACWY+ group, 3% in the PS Stage 1 group (headache = 3%), 5% in the MenACWY- group (headache = 5%, malaise = 2%), and 3% in the PS Stage 2 group (malaise and chills = 3%).

Overall, the rates of severe local or systemic reactogenicity were low in all groups (less than 7% in the MenACWY groups and less than 4% in the Menomune groups) and of limited duration (all resolved completely or decreased in intensity within 2 days after onset).

Among the 524 subjects included in the safety database, 70 of 164 (43%) MenACWY+ subjects, 65 of 170 (38%) PS Stage 1 subjects, 79 of 151 (52%) MenACWY- subjects, and 17 of 39 (44%) PS Stage 2 subjects reported at least one adverse event during the study. These figures indicate that the incidence of treatment-emergent AEs was similar among the four vaccine groups.

No deaths were reported during this study.

A total of 13 subjects reported 15 SAEs (MenACWY+: four subjects, 2%; PS Stage 1: five subjects, 3%; MenACWY-: two subjects, 1%; PS Stage 2: two subjects, 5%). None of the reported SAEs was considered by the investigator to be related to vaccine treatment. All but two of the reported SAEs (road traffic accident and ventricular tachycardia) had resolved by the end of the study.

SAEs in MenACWY subjects were pharyngeal cellulitis (MenACWY+), supraventricular tachycardia (MenACWY+), facial bones fracture (MenACWY+), hepatitis (MenACWY-), and femur fracture (MenACWY-). SAEs in Menomune subjects were postoperative wound infection (PS Stage 1), appendicitis (PS Stage 1), lower abdominal pain (PS Stage 1), arachnoid cyst (PS Stage 1), wound infection (PS Stage 1), hand fracture (PS Stage 1), auditory hallucination (PS Stage 2), and appendicitis (PS Stage 2).

No AEs were reported that lead to a premature withdrawal of the subject from the study.

Conclusions

In this phase 2, randomized, single-blind, controlled, multicenter study comparing the safety and immune response of one dose of MenACWY conjugate vaccine with

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(MenACWY+) and without (MenACWY-) aluminum phosphate adjuvant with one dose of Menomune vaccine administered to healthy adolescents 11 to 17 years of age, the immunogenicity profile of the MenACWY+ and MenACWY- groups was noninferior to the Menomune group.

A single dose of MenACWY+ or MenACWY- was well tolerated by healthy adolescents 11 to 17 years of age. Overall, the pattern of significant AEs and SAEs in the MenACWY subjects was not inconsistent with what would be expected within this age group. None of the SAEs were considered by the investigator to be related to study vaccine administration.

Table 2-1 Time and Events

Visit Number **Study Day**	**1** **1**	**☎** **3**	**2** **29**	**☎** **180**	**3** **360**
(Range)	**(1)**	**(2 to 4 days after Visit 1)**	**(28 to 35 days after Visit 1)**	**(164 to 194 days after Visit 1)**	**(344 to 374 days after Visit 1)**
Procedures					
Obtain Informed Consent	x				
Medical History	x				
Physical Examination [a]	x		x		x
Obtain Blood Sample	x		x		x
Administer Study Vaccine [b]	x				
Injection-site Examination [c]	x		x		x
Assess Local and Systemic Reactions [d]	x		x		
Concomitant Medications	x [e]	x [e]	x [f]		x [f]
Adverse Events [g]	x	x	x	x	x
Study Termination					x

[a] The physical examinations at visits 1, 2, and 3 (study days 1, 29, and 360) was to be performed by a study physician or a designated study nurse.

[b] The study vaccine, MenACWY conjugate vaccine was to be administered IM into the subjects left deltoid muscle; the control vaccine, a licensed meningococcal vaccine, Menomune®, was to be administered SC into the subject's left upper arm. All subjects were to be observed in the clinic for 30 minutes after vaccination.

[c] Inspect the injection site at all study visits.

[d] Local and systemic reactions following vaccination were to be noted by subjects in the diary cards daily for 7 days after vaccination (study days 1 through 7). The diary cards were to be reviewed during the day 3 follow-up phone interview and collected at visit 2.

[e] Collect data on concomitant medications (prescription and nonprescription) through the first 7 days.

[f] Collect data on concomitant medications (prescriptions only) from day 8 through visit 3.

[g] From day 1 through day 7, record and collect information regarding all AEs. From day 8 up to visit 2, record and collect information regarding any SAE, any event requiring a medical office visit, and any event resulting in a subject's early termination. From visit 2 through visit 3, record and collect any SAE, any significant medical event, and any event resulting in a subject's early termination.

Note: Day 1 was defined as day of study vaccination.

Table 2-2 Percent of Subjects With hSBA ≥ 1:4 at 1 Month After Vaccination With Novartis MenACWY or Menomune

Sero-group	Time of blood sample	n (%) 95%CI[a], N[b]	MenACWY +	MenACWY-	Menomune	*P* values
A	Prevaccination	n (%) 95% CI N	3 (2) 0-5 158	2 (1) 0-5 148	5 (3) 1-6 179	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	137 (87)[C] 80-92 158	124 (84)[D] 77-89 148	82 (46)[C,D] 38-53 179	C < .001*** D < .001***
	censored 1 month after vaccination	n (%) 95% CI N	134 (86)[C] 80-91 155	122 (84)[D] 77-89 146	78 (45)[C,D] 37-53 174	C < .001*** D < .001***
C	Prevaccination	n (%) 95% CI N	43 (27) 20-34 161	36 (24) 18-32 148	48 (27) 21-34 177	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	149 (93)[C] 87-96 161	130 (88)[D] 81-93 148	126 (71)[C,D] 64-78 177	C < .001*** D < .01**
	censored 1 month after vaccination	n (%) 95% CI N	106 (90)[C] 83-95 118	94 (84)[D] 76-90 112	79 (61)[C,D] 52-70 129	C < .001*** D < .001***
W	Prevaccination	n (%) 95% CI N	70 (43)[C] 36-52 161	19 (13)[D] 8-20 146	41 (24)[C,D] 18-31 173	C < .001*** D = .012*
	1 month after vaccination	n (%) 95% CI N	157 (98)[C] 94-99 161	139 (95)[D] 90-98 146	153 (88)[C,D] 83-93 173	C < .001*** D =.024*
	censored 1 month after vaccination	n (%) 95% CI N	87 (96)[C] 89-99 91	120 (94)[D] 89-98 127	112 (85)[C,D] 78-90 132	C = .005** D = .010**
Y	Prevaccination	n (%) 95% CI N	41 (26) 19-33 159	40 (27) 20-35 147	49 (28) 21-35 177	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	154 (97)[C] 93-99 159	141 (96)[D] 91-98 147	148 (84)[C,D] 77-89 177	C < .001*** D < .001***
	censored 1 month after vaccination	n (%) 95% CI N	113 (96)[C] 90-99 118	101 (94)[D] 88-98 107	100 (78)[C,D] 70-85 128	C < .001*** D < .001***

[a] CI=confidence interval
[b] N=number of subjects
C = comparison between MenACWY+ and Menomune
D = comparison between MenACWY- and Menomune
Data sources: Tables 14.2.1.1 and 14.2.1.1.1.
*$P < .05$, **$P < .01$, ***$P < .001$

Table 2-3 Percent of Subjects With hSBA ≥ 1:8 at 1 Month After Vaccination With Novartis MenACWY or Menomune

Sero-group	Time of blood sample	n (%) 95%CI[a], N[b]	MenACWY +	MenACWY-	Menomune	*P* values
A	Prevaccination	n (%) 95% CI N	2 (1) 0-4 158	2 (1) 0-5 148	1 (1) 0.014-3 179	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	128 (81)[C] 74-87 156	120 (81)[D] 74-87 148	74 (41)[C,D] 34-49 179	C < .001*** D < .001***
	censored 1 month after vaccination	n (%) 95% CI N	126 (81)[C] 74-87 156	118 (81)[D] 73-87 146	73 (41)[C,D] 34-49 174	C < .001*** D < .001***
C	Prevaccination	n (%) 95% CI N	20 (12) 8-19 161	25 (17) 11-24 148	32 (18) 13-25 177	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	138 (86)[C] 79-91 161	123 (83)[D] 76-89 148	112 (63)[C,D] 56-70 177	C < .001*** D < .001***
	censored 1 month after vaccination	n (%) 95% CI N	118 (84)[C] 77-89 141	98 (80)[D] 71-86 123	80 (55)[C,D] 47-63 145	C < .001*** D < .001***
W	Prevaccination	n (%) 95% CI N	66 (41)[C] 33-49 161	19 (13)[D] 8-20 146	37 (21)[C,D] 16-28 173	C < .001*** D = .045*
	1 month after vaccination	n (%) 95% CI N	156 (97)[C] 93-99 161	132 (90)[D] 84-95 146	149 (86)[C,D] 80-91 173	C < .001*** D > .05
	censored 1 month after vaccination	n (%) 95% CI N	90 (95)[C] 88-98 95	113 (89)[D] 82-94 127	112 (82)[C,D] 75-88 136	C = .002* D > .05
Y	Prevaccination	n (%) 95% CI N	28 (18) 12-24 159	34 (23) 17-31 147	40 (23) 17-29 177	*P* > .05 each pairwise test
	1 month after vaccination	n (%) 95% CI N	149 (94)[C] 89-97 159	139 (95)[D] 90-98 147	143 (81)[C,D] 74-86 177	C < .001*** D < .001***
	censored 1 month after vaccination	n (%) 95% CI N	121 (92)[C] 86-96 131	105 (93)[D] 87-97 113	104 (76)[C,D] 68-83 137	C < .001*** D < .001***

[a] CI=confidence interval
[b] N=number of subjects
C = comparison between MenACWY+ and Menomune
D = comparison between MenACWY- and Menomune
Data sources: Tables 14.2.1.2 and 14.2.1.2.1.
*$P < .05$, **$P < .01$, ***$P < .001$

Table 2-4 Percentage of Subjects with hSBA Titers ≥ 1:4 at 1 and 12 Months After Vaccination

Sero-group	% 95% CI[a], N[b]	MenACWY-	Menomune	*P* values
A	1 mo % 95% CI N	84 77 - 90 140	46 38 - 55 149	< .001***
	12 mo % 95% CI N	36 28 - 44 140	44 36 - 53 149	.043
C	1 mo % 95% CI N	89 82 - 93 140	69 61 - 76 147	< .001***
	12 mo % 95% CI N	86 79 - 91 140	69 61 - 76 147	< .001***
W	1 mo % 95% CI N	95 90 - 98 138	87 80 - 92 141	.016*
	12 mo % 95% CI N	95 90 - 98 138	72 63 - 79 141	< .001***
Y	1 mo % 95% CI N	96 93 - 99 139	85 78 - 90 147	.001**
	12 mo % 95% CI N	87 80 - 92 139	63 54 - 70 147	< .001***

[a] CI=confidence interval

[b] N=number of subjects per group who have results before, at 1 month, and at 12 months after vaccination.

Data source: Tables 14.2.1.5 and 11.4.1.1.2-2.

*P < .05, **P < .01, ***P < .001

Table 2-5 hSBA GMTs at 1 Month and 12 Months After Vaccination

Sero-group	95%CI[a], N[b]	MenACWY-	Menomune	*P* values
A	1 mo GMT 95% CI N	33 25 - 44 140	7.31 5.64 - 9.47 149	< .001***
	12 mo GMT 95% CI N	4.24 3.35 - 5.38 140	5.65 4.54 - 7.03 149	.086
C	1 mo GMT 95% CI N	59 39 - 89 140	28 19 - 41 147	.005**
	12 mo GMT 95 % CI N	28 19 - 41 140	26 18 - 37 147	.77
W	1 mo GMT 95% CI N	48 37 - 62 138	28 23 - 36 141	.001**
	12 mo GMT 95% CI N	40 31 - 52 138	17 13 - 22 141	< .001***
Y	1 mo GMT 95% CI N	92 68 - 124 139	35 27 - 47 147	< .001***
	12 mo GMT 95% CI N	30 22 - 41 139	13 9.49 - 17 147	< .001***

[a] CI=confidence interval
[b] N=number of subjects per group who have results before, at 1 month, and at 12 months after vaccination.

Data sources: Tables 14.2.1.7 and 11.4.1.1.2-3.
*$P < .05$, **$P < .01$, ***$P < .001$

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P7**	

Title of study: A Phase II, Randomized, Observer Blind, Multi-Center, Active Controlled Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Children Aged 12 to 59 Months.

Protocol number: V59P7

Investigators: Prof. Timo Vesikari, MD, Ryszard Konior, MD, PhD; Jerzy Dziduch, MD

Study centers: University of Tampere Medical School, Tampere, Finland; Oddz. Neuroinfekcji, Szpital Jana Pawla II, Kraków, Poland; Samodzielny ZOZ, Lubartów, Poland

Publication (reference): none

Study period: 14 March 2005 – 16 May 2006	**Phase of development:** Phase 2

Objectives:

Immunogenicity Objectives

Primary

For subjects aged 36 to less than 60 months

- To compare the functional immune response 28 days after administration of one dose of MenACWY conjugate vaccine without adjuvant (Ad-) with that of a MenACWY polysaccharide (PS) vaccine, as measured by the percentage of subjects with human complement serum bactericidal activity (hSBA) ≥1:4 against *N meningitidis* serogroups A, C, W, and Y.

Secondary

- To compare the functional immune response 28 days after administration of one dose of MenACWY Ad- with that of a MenACWY PS vaccine, as measured by hSBA geometric mean titers (GMTs) and hSBA ≥1:8 against *N meningitidis*

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serogroups A, C, W, and Y.

In addition, the following secondary objectives were to be evaluated using hSBA GMTs and percentage of responders with hSBA titers ≥1:4 and ≥1:8:

- The persistence of functional immune response at 6 or 12 months following administration of one dose of either MenACWY Ad- or MenACWY PS vaccine.
- The booster effect 21 days after one dose of MenACWY Ad- vaccine administered 6 or 12 months after the first dose of either MenACWY Ad- or MenACWY PS vaccine.

For subjects aged 12 to less than 36 months

The following secondary objectives were to be evaluated using hSBA GMTs and percentage of responders with hSBA titers ≥1:4 and ≥1:8:

- The functional immune response 28 days after administration of one dose of either MenACWY conjugate vaccine with adjuvant (Ad+) or MenACWY Ad-.
- The functional immune response 21 days after a second dose of either MenACWY Ad+ or MenACWY Ad- administered 1 month after the first dose.
- The persistence of functional immune response at 6 or 12 months following administration of one dose of either MenACWY Ad+ or MenACWY Ad-.
- The persistence of functional immune response at 12 months following administration of two doses of either MenACWY Ad+ or MenACWY Ad-.
- The booster effect 21 days after a second dose of either MenACWY Ad+ or MenACWY Ad- administered at 6 or 12 months after the first dose.

Safety Objective

For all subjects aged 12 to less than 60 months

- To evaluate the safety and tolerability of MenACWY Ad+ or MenACWY Ad- or MenACWY PS when administered to healthy children 12 to less than 60 months old.

Methodology:

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Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W_{135}-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P7**	

This was a phase II, multicenter, controlled, randomized, observer blind study conducted in Finland and Poland.

A total of approximately 600 healthy subjects aged 12 to less than 60 months were to be allocated into one of four vaccination groups according to their specific age: toddlers aged 12 to 35 months were randomized to MenACWY Ad+ or MenACWY Ad-, and children aged 36 to 59 months were randomized to MenACWY Ad- or MenACWY PS (and received MenACWY Ad- as the second vaccination).

The groups of toddlers were further divided into two subgroups according to their age, i.e., either 12 to 24 months or 25 to 35 months of age.

Vaccination Group	**Treatment and Number of Subjects Planned**			
	First Vaccination	**Second vaccination**		
	Day 1	**1 Month**	**6 Months**	**12 Months**
Toddlers aged 12-35 months*	MenACWY Ad+ N=200	MenACWY Ad+ N=66		
			MenACWY Ad+ N=66	
				MenACWY Ad+ N=66
Toddlers aged 12-35 months*	MenACWY Ad- N=200	MenACWY Ad- N=66		
			MenACWY Ad- N=66	
				MenACWY Ad- N=66
Children aged 36-59 months	MenACWY Ad- N=100		MenACWY Ad- N=50	
				MenACWY Ad- N=50
Children aged 36-59 months	MenACWY PS N=100		MenACWY Ad- N=50	
				MenACWY Ad- N=50

*Groups of toddlers aged 12 to 35 months were divided into two subgroups: toddlers aged 12 to 24 months, and toddlers aged 25 to 35 months

Toddlers aged 12 to 35 months received one intramuscular (IM) dose of MenACWY Ad+ or Ad- on day 1; each group was divided in three subsets of approximately 66 subjects each, who received a second dose of the same vaccine at 1, 6, or 12 months

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their second vaccination at 6 or 12 months, respectively. Subjects, who received the second vaccination at 1 month after the first dose of vaccination, were evaluated for persistence at 12 months after the first vaccination.

Children aged 36 to 59 months received one IM dose of MenACWY Ad- or MenACWY PS on day 1; each group was divided in two subsets of 50 subjects each, who received a second dose of MenACWY Ad- (both groups) at 6 or 12 months after the first dose, respectively.

Blood was collected at visit 1 (day 1, prior to vaccination) and at visit 2 (28 days after visit 1) in all subjects. In addition blood samples were taken prior to and 21 days after the second vaccination. In subjects who received the second vaccination on day 29, an additional blood sample was taken at visit 4 (357 days after visit 1).

The subjects remained in the clinic for 30 minutes after each vaccination to monitor for any hypersensitivity reactions and other adverse events (AEs). A diary card was completed to describe local (i.e., tenderness, erythema, induration) and systemic reactions (i.e., change in eating habits, sleepiness, vomiting, diarrhea, and irritability) for 7 days following each vaccination. During this period, axillary or rectal temperature (based on local routine practice and subject's age) were also recorded daily.

Number of subjects (planned and analyzed):

Approximately 600 subjects were planned to be recruited in the study centers in Finland and Poland, 623 were actually enrolled; 617 subjects were exposed to study vaccine and included in the safety analysis, 574 were included in the immunogenicity analysis.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion criteria

Subjects eligible for enrollment in the study were healthy 12 to less than 60-month-old children, for whom a parent/legal guardian had given written informed consent after the nature of the study had been explained. They were to be available for all the visits scheduled in the study and in good health as determined by: medical history, physical examination, and clinical judgment of the investigator.

Exclusion criteria are given in section 9.3.2.

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Test product, dose, mode of administration, lot number:

The investigational Novartis MenACWY Conjugate Vaccine with adjuvant (aluminum phosphate 0.3 mg Al^{3+}) and without adjuvant was obtained by extemporaneous mixing, just before injection, of the lyophilized MenA component to be resuspended with the MenCWY liquid component. After reconstitution, MenACWY Conjugate Vaccine had the following composition per 0.5 mL of injectable suspension (for the full list of components refer to section 9.4.2):

CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
In addition for MenACWY with adjuvant (Ad+)	
Aluminum phosphate	0.3 mg Al^{3+}

CRM = cross-reactive material

The following batch numbers were used in the study: Chiron MenA 002011, Chiron MenCWY (with adjuvant) U79P32D1, Chiron MenCWY (without adjuvant) U79P33D1. Vaccines were administered IM in the deltoid region.

Duration of study:

Each subject received two injections of study vaccine: the first on day 1 and the second on day 29, 169, or 337. Subjects returned to the clinic at 4 weeks after the first and at 3 weeks after the second vaccination for post vaccination assessments. Toddlers, who received the second vaccination on day 29, returned for an additional post vaccination assessment on day 358. Safety follow-up was performed for 6 months after the second vaccination.

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Reference therapy, dose, mode of administration, lot number:

One injection of a licensed tetravalent meningococcal ACWY PS vaccine (GSK Mencevax™* ACWY, commercially available lots) was administered IM in the deltoid region.

The licensed GSK Mencevax vaccine contained 50 µg of plain polysaccharide from each of four meningococcal serogroups (A, C, W, and Y) in a single 0.5 mL dose.

Criteria for evaluation:

Immunogenicity

Serum bactericidal activity (SBA) was measured for each serogroup using human serum as the source of complement (hSBA) and then expressed as geometric mean titer (GMT) and percentage of subjects with hSBA titer ≥ 1:4 (% ≥ 1:4) and ≥ 1:8 (% ≥ 1:8).

Safety

Measures of safety and reactogenicity included data from observed local reactions and systemic reactions.

These data were collected together with axillary or rectal temperature, analgesic or antipyretic medication use, and all other AEs during the first 7 days after each injection. Thereafter only serious adverse events (SAE), AEs necessitating a physician's visit and/or resulting in premature withdrawal of subjects from the study were collected. A follow up safety phone call was performed 6 months after the last vaccination to assess for any SAE and any other medically significant AEs.

Statistical methods:

There were no formal statistical (null) hypotheses associated with the immunogenicity objectives; the data were summarized descriptively. At each time point, hSBA GMTs and 95% confidecen interval (CI) and the percentage of subjects with hSBA titers ≥1:4 and ≥ 1:8 were calculated. The GMTs and geometric mean ratios of post-vaccination to pre-vaccination GMT (GMRs) and two-sided 95% CIs and median, minimum, and

* Mencevax is a registered trademark of GlaxoSmithKline

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maximum values were calculated for each vaccine group and for each serogroup by exponentiating (base 10) the least square means of the logarithmically transformed (base 10) titers and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine group and country. Titers below the limit of detection were set to half that limit for the purposes of the analysis. The percentages of responders and associated two-sided 95% Clopper-Pearson CIs were computed for each of the three vaccine groups within each serogroup.

Summary and Conclusions:

Immunogenicity results

A total of 623 subjects were enrolled in this study. One hundred eighty two (182) of the 210 children aged 36 to 59 months randomized to MenACWY Ad- (101 subjects) or MenACWY PS vaccine (81 subjects) were included in the PP population of the first vaccination; 160 of the 194 children, who received the second vaccination with MenACWY Ad- 6 or 12 months later (93 in the MenACWY Ad- and 67 in the MenACWY PS group) were included in the PP population of the second vaccination.

Three hundred ninety two (392) of the 413 toddlers aged 12 to 35 months randomized to receive MenACWY conjugate vaccine with or without adjuvant (200 MenACWY Ad+ and 192 MenACWY Ad-) were included in the PP population of the first vaccination; 334 of the 401 toddlers, who received a second dose of the same vaccine (174 MenACWY Ad+ and 160 MenACWY Ad-), were included in the PP population of the second vaccination.

Overall, the PP population comprised 92% of the enrolled population. Baseline and other demographic characteristics were generally balanced between the vaccine groups.

Children aged 36 to 59 months

The primary objective of the study was to compare the functional immune response 28 days after administration of one dose of MenACWY conjugate vaccine without adjuvant (Ad-) with that of a MenACWY PS vaccine administered to subjects aged 36 to 59 months, measured by the percentage of subjects with hSBA ≥1:4 against serogroups A, C, W, and Y. At one month after vaccination the percentage of subjects with hSBA titers ≥ 1:4 was higher in the MenACWY Ad- group than in the MenACWY PS group

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for all serogroups (60% to 91% of subjects in the MenACWY Ad- had a titer ≥1:4 and 52% to 67% in the MenACWY PS group).

Similar results were obtained for the other immunogenicity parameters: the percentage of subjects with hSBA titers ≥ 1:8 was higher in the MenACWY Ad- group than in the MenACWY PS group (54% to 84% for MenACWY Ad-and 39% to 59% for MenACWY PS for the different serogroups) and GMTs increased more pronounced in the MenACWY Ad- group for serogroups A, W, and Y compared to baseline (GMR between 7.11 and 8.75 for MenACWY Ad-, and between 3.37 and 5.84 for MenACWY PS), whereas no relevant difference was observed for serogroup C (2.94 and 2.82 after MenACWY Ad- and MenACWY PS, respectively).

Persistence and the effect of the booster vaccination at 6 and 12 months after the first vaccination were only evaluated for subjects of the MenACWY Ad- group.

In the MenACWY Ad- group, persistence showed no relevant differences at 6 and 12 months after the first vaccination. Generally persistence was low for serogroup A (23% and 13% of the subjects, respectively, had an hSBA titer ≥ 1:4, GMR had returned close to day 1 baseline levels). In contrast, hSBA levels were maintained at 6 and 12 months post vaccination for serogroups W and Y, and were only moderately lower for serogroup C. Evaluation of the percentage of subjects with hSBA titer ≥1:8 and of GMT gave similar conclusions.

At 21 days after the second vaccination the percentage of subjects with an hSBA titer ≥1:4 was 100% for serogroups C, W, and Y, independent of the time period between the first and second vaccination. For serogroup A the percentages of subjects were 90% (second vaccination after 6 months) and 98% (second vaccination after 12 months).

Similar results were obtained using the hSBA titer ≥1:8 as a responder criterion. GMTs and GMRs were higher for all serogroups in children receiving the second vaccination at 12 months compared to those vaccinated at 6 months (2.5- to 4.4-fold higher in the 12 month group).

In conclusion, the immune response 28 days after vaccination was higher in subjects who received MenACWY Ad- compared to those who received MenACWY PS. SBA

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levels persisted at 6 and 12 months after vaccination with MenACWY Ad- for serogroups C, W, and Y, but declined for serogroup A. A second vaccination with MenACWY Ad- at 6 or 12 months after the first vaccination with MenACWY Ad- showed a robust booster response for all serogroups, which was higher when the interval for vaccination was 12 months compared to 6 months. These results provide evidence that a single dose of MenACWY in children can effectively induce immunologic memory.

Toddlers aged 12 to 35 months

Overall there were no relevant differences in immunogenicity results between the subgroups of toddlers aged 12 to 24 and 25 to 35 months; therefore, only the results of the whole group of toddlers aged 12 to 35 months are described.

Secondary immunogenicity analyses included the evaluation of the functional immune response 28 days after administration of one dose of either MenACWY Ad+ or MenACWY Ad-. The percentage of subjects with hSBA titers ≥ 1:4 was slightly higher in the MenACWY Ad+ group than in the MenACWY Ad- group for serogroups A and C (82% in the MenACWY Ad+ group and 70% in the MenACWY Ad- group for serogroup A and 56% and 49%, respectively, for serogroup C), and was similar for serogroups W and Y (82% and 80%, respectively, for serogroup W and 67% for both vaccination groups for serogroup Y). A similar trend was seen when using an hSBA titer ≥ 1:8, GMTs and GMRs for analysis of the immune response.

Persistence and the effect of the booster vaccination at 1, 6, and 12 months after the first vaccination were only evaluated for subjects of the MenACWY Ad- group.

Administration of a second dose of MenACWY Ad- at 1 month after the first vaccination resulted in further increases in the percentage of subjects achieving an hSBA titer ≥1:4 for all serogroups compared to the first dose (hSBA ≥1:4 ranged between 91% and 98% of subjects for all serogroups at 3 weeks after the second vaccination vs. 49% to 80% following the first vaccination). Similar results were obtained when using the hSBA titer ≥1:8 as a cut-off. Further increases in GMTs were also achieved compared to the first dose, and GMRs ranged from 3.29 (serogroup A) to

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13 (serogroup C).

Persistence in the immune response was determined prior to the second vaccination administered at 6 or 12 months after the first vaccination. Generally the persistence of hSBA was low for serogroup A, but for the other serogroups the hSBA levels at 6 months after vaccination were similar to the response at 28 days after the first vaccination and slightly lower at 12 months after vaccination.

In a subgroup of toddlers aged 12 to 35 months, who received a second vaccination with MenACWY Ad- at 1 month after the first vaccination, persistence was determined 1 year after the first vaccination. A marked decrease in the percentage of subjects with an hSBA titer ≥1:4 was observed for serogroup A: from 92% of the subjects who were responders at 21 days after the second vaccination to only 29% at 1 year after the first vaccination. For the other serogroups the decrease in the number of subjects with hSBA titer ≥1:4 was smaller as the majority of subjects still maintained an hSBA titer ≥1:4 at the end of 1 year (73%, serogroup C; 87%, serogroup W; 81%, serogroup Y). Similar trends were obtained when using an hSBA titer ≥1:8. Except for serogroup A, GMTs remained higher 1 year after the second dose compared to the GMTs 28 days after the first dose.

Booster vaccination at 6 or 12 months after the first vaccination resulted in a robust immune response at 21 days after the second vaccination. Nearly all toddlers achieved an hSBA titer ≥1:4 for the four serogroups: 95% for serogroup A and 100% for the other serogroups after the second vaccination at 6 months and 96% for serogroups A and C, and 100% for serogroups W and Y after the second vaccination at 12 months. The results were similar when using an hSBA titer ≥1:8. The GMTs determined 21 days after the second vaccination were always consistently higher in the group of subjects who received the second vaccination at 12 months after first vaccination. The GMR for all serogroups ranged between 25 (serogroup A) and 37 (serogroup W) in the group who received the second vaccination at 6 months, and ranged between 70 (serogroup A) and 151 (serogroup W) in the group who received the second vaccination at 12 months.

In conclusion, vaccination with MenACWY Ad+ or MenACWY Ad- resulted in similar

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immune responses in toddlers 12 to 35 months of age, although the GMR for serogroups A and C were slightly higher in the MenACWY Ad+ group compared to the MenACWY Ad- group. The second vaccination with MenACWY Ad- showed very robust immune responses with the highest responses observed in subjects administered the second dose 12 months after the first. These results are again consistent with the induction of immunologic memory in toddlers following a single dose of MenACWY. Except for serogroup A, hSBA persisted in a high proportion of subjects at 6 or 12 months after the first vaccination. Following two doses of MenACWY Ad- in toddlers, hSBA persisted in the majority of subjects at 1 year post first dose for serogroups C, W, and Y.

Safety results

A total of 623 subjects were enrolled in this study, 210 children aged 36 to 59 months and 413 toddlers aged 12 to 35 months. Two hundred and six (206) children received the first vaccination (125 in the MenACWY Ad- and 81 in the MenACWY PS group), and 194 children received the second vaccination (120 in the MenACWY Ad- and 74 in the MenACWY PS group that received MenACWY Ad- as a second vaccination). Four hundred eleven (411) toddlers received the first vaccination (205 in the MenACWY Ad+ and 206 in the MenACWY Ad- group), and 401 toddlers received the second vaccination (200 MenACWY Ad+ and 201 MenACWY Ad-).

Overall, the percentages of subjects reporting solicited AEs during the 7 days after vaccination were similar for all four vaccination groups and, for all groups, slightly lower after the second vaccination compared to the first vaccination (first vaccination: 56% to 62%, second vaccination: 43% to 52%).

The incidence of local reactions was independent of the age group. The highest incidence of local reactions was observed in the group of subjects that received the MenACWY PS vaccine (53% versus 38% to 45% after MenACWY Ad+ or Ad-). After the second vaccination, when all subjects received either MenACWY Ad+ or MenACWY Ad-, the percentage of subjects with local reactions showed no relevant differences between the vaccine groups (35% to 38%). The most frequently reported local reaction was tenderness, reported by 24% to 29% of the toddlers aged 12 to 35

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months, irrespective of the vaccine and the vaccination number. In the group of children, tenderness was more frequently reported for subjects who received MenACWY PS (46% of the children, compared to 31% to 33% after MenACWY Ad- administered as first or second vaccination). Tenderness of severe intensity was infrequent and mainly occurred in the toddlers receiving MenACWY Ad+ and in the children receiving MenACWY PS. Almost all local reactions started within the first 3 days after vaccination. There were only 3 reports of local reactions that started later than day 3.

Systemic reactions were less often reported for children aged 36 to 59 months (14% to 29% of the subjects) compared to toddlers aged 12 to 35 months (30% to 38% of the subjects). The most commonly reported systemic reactions were irritability, sleepiness and change in eating habits. There were no clinically significant differences between toddlers receiving MenACWY Ad+ and MenACWY Ad- or between children receiving MenACWY Ad- and MenACWY PS. The incidence of systemic reactions was generally lower after the second vaccination compared to the first vaccination. Irritability and sleepiness, the most frequently reported systemic reactions, were reported mainly in the 3 days immediately following vaccination. One child experienced fever ≥ 40°C after vaccination with MenACWY PS.

Solicited adverse events were mainly of mild intensity and resolved in most subjects during the 7-day post vaccination period.

The percentage of subjects reporting unsolicited AEs was similar among the four vaccine groups (57% and 48% of the toddlers and 51% for both children groups). Generally lower percentages of subjects reported AEs after the second vaccination (onset between day 1 and day 21 after the second vaccination, 16% to 20% of the subjects of all four vaccination groups) compared to the first vaccination (onset between day 1 and day 29 after the first vaccination, 32% to 38% of the subjects).

The most frequently reported AEs were under the MedDRA system organ class (SOC) 'infections and infestations' (e.g., upper respiratory tract infection), which were reported by a similar percentage of subjects in all four vaccination groups (35% to 43% of the subjects in all four vaccination groups).

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Most unsolicited AEs were of mild to moderate intensity. AEs of severe intensity were reported by 1% to 5% of the subjects in the different vaccination groups. All severe AEs, except one, were considered as not vaccine-related by the investigator. Severe injection site erythema was reported for one child in the MenACWY Ad- group.
Most AEs were considered as not vaccine-related by the investigator. Possibly or probably related AEs were reported by 1% to 4% of the subjects in the four vaccination groups. Vaccine-related AEs started within 7 days after vaccination; only one episode each of injection site erythema, irritability, erythema, and pruritus occurred in three subjects (two toddlers in the MenACWY Ad+ and one child in the MenACWY Ad- group) and started later than day 7.

Vaccine-emergent AEs led to premature withdrawal of four subjects from the study; all of these subjects were in the toddler age group and the reasons for withdrawal were: brain neoplasm, nervous system disorder and asthma (all three subjects in the MenACWY Ad+, study day 38, day 79 and day 108 post vaccination, respectively) and febrile convulsions (one subject in the MenACWY Ad- group, study day 20).

No deaths occurred during this study. SAEs were reported for 45 subjects during this study (6% of the toddlers in both the MenACWY Ad+ and the MenACWY Ad- group, 9% of the children in the MenACWY Ad- group and 11% of the children in the MenACWY PS group). The majority of SAEs were under the MedDRA SOC 'infections or infestations' (mainly varicella infections). Varicella was reported for 26 subjects (six subjects each in the group of toddlers who received MenACWY Ad+ and in both children groups, and eight subjects in the MenACWY Ad- group). Varicella was reported as mild (20 SAEs), moderate (4 SAEs), or severe in intensity (2 SAEs). Most SAEs occurred in the period between the first and second vaccination and did not show any temporal association with the vaccination. All SAEs were considered as not vaccine related. The only SAE leading to premature withdrawal from the study was brain neoplasm (one toddler in the MenACWY Ad+ group).

Conclusions

The functional immune response, as measured by hSBA, in children aged 36 to 59 months at 28 days after vaccination was higher in subjects who received MenACWY

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Ad- compared to those who received MenACWY PS for all serogroups. Levels of hSBA at 6 and 12 months after vaccination with MenACWY Ad- declined for serogroup A and were moderately lower for serogroup C, but persisted for serogroups W and Y compared to 28 days after the first vaccination. A second booster vaccination with MenACWY Ad- at 6 or 12 months after the first dose showed very robust responses (>90% achieving an hSBA titer ≥1:4 for all serogroups), with GMTs higher in subjects who received the second dose at 12 months.

Vaccination with MenACWY Ad+ or MenACWY Ad- to toddlers aged 12 to 35 months resulted in similar immune responses across the four serogroups, although the GMRs for serogroups A and C were slightly higher in the MenACWY Ad+ group compared to the MenACWY Ad- group. The second vaccination with MenACWY Ad- showed good booster responses (>90% achieving an hSBA titer ≥1:4 for all serogroups) with the highest responses in subjects administered the second dose 12 months after the first. Persistence of hSBA at 6 or 12 months after the first vaccination was generally low for serogroup A, but higher for serogroups C, W, and Y. Following two doses of MenACWY Ad- in toddlers, hSBA persisted in the majority of subjects at 1 year post first dose for serogroups C, W, and Y (hSBA > 70%) and declined for serogroup A (29%).

The strong booster responses observed at 6 and 12 months after the first dose of MenACWY demonstrate that a single dose of MenACWY can effectively induce immunologic memory in both toddlers and young children. The ability to induce B cell memory, in turn, supports the concept that each of the conjugated serogroup oligosaccharides in the vaccine is acting as a T-cell dependent immunogen.

Both MenACWY Ad+ and Ad- were well tolerated with a lower local reactogenicity profile compared to MenACWY PS. No unexpected unsolicited or otherwise clinically significant AEs related to the vaccines administered were reported in this study. No deaths occurred in the study.

Table 2-1 Time and Events Schedule

DAY (window)	**1**	3/8 (+2)	29 (+7)	31/36 (+2)	50 (±7)	169 (±7)	171/ 176 (+2)	190 (±7)	337 (±7)	339/ 344 (+2)	358 (±7)	6 months (±15)
VISIT N°	1	☎	2	☎(1)	**3**(1)	**3** (2)	☎(2)	**4** (2)	**3**(3)	☎(3)	**4**	☎(4)
Informed consent	X											
Medical history	X											
Physical examination	X		X		X	X		X	X		X(3) (1)	
Screen for inclusion/ exclusion criteria	X		X(1)			X			X			
Follow-up telephone call		X		X			X			X		X
Serology	X		X		X	X		X	X		X(3) (1)	
Axillary/rectal temperature	X	X	X(1)	X		X	X		X	X		
Administration of vaccine	X		X(1)			X			X			
Injection-site examination	X		X(1)			X			X			
Local/systemic reactions	X	X	X(1)	X		X	X		X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X((3)1)	
Adverse events	X	X	X	X	X	X	X	X	X	X	X(3) (1)	X
Diary card review			X		X			X			X(3)	
Complete Study Termination CRF								X			X(3) (1)	

Note: Day 1 was defined as day of first study vaccination.
X for all enrolled subjects

(1) this visit/phone call/measurement was applicable only to the 1st subsets of children aged 12 to less than 36 months (groups I and II).
(2) this visit/phone/measurement call was applicable only to the 2nd subsets of children aged 12 to less than 36 months (groups I and II) and to the 1st subset of children aged 36 to less than 60 months (groups III and IV).
(3) this visit/phone call/measurement was applicable only to the 3rd subsets of children aged 12 to less than 6 months (groups I and II) and to the 2nd subset of children aged 36 to less than 60 months (groups III and IV).
(4) A follow up safety phone call was performed 6 months after any vaccination or subject's withdrawal.

Table 2-2 Primary Immunogenicity Variable: Percentage of Subjects (95% CI) 36 to 59 Months Old with hSBA Titer ≥ 1:4 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[b]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
A	2% (0-7)	1% (0.032-7)	75% (66-83)	55% (43-66)	23% (12-37)	92% (80-98)	13% (5-27)	98% (88-100)
C	14% (8-23)	10% (4-19)	60% (49-69)	52% (40-63)	45% (30-60)	100% (92-100)	42% (28-58)	100% (92-100)
W	17% (10-26)	19% (11-29)	91% (84-96)	67% (55-77)	94% (82-99)	100% (92-100)	84% (71-94)	100% (92-100)
Y	10% (5-18)	11% (5-21)	77% (68-85)	67% (56-77)	70% (55-83)	100 (92-100)	80% (65-90)	100% (92-100)

[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.1 and Table 14.2.1.3

Table 2-3 Secondary Immunogenicity Variable: Percentage of Subjects (95% CI) 36 to 59 Months Old with hSBA Titer ≥ 1:8 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[b]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
A	2% (0-7)	0% (0-5)	61% (51-71)	39% (28-50)	10% (3-23)	90% (77-97)	9% (2-21)	98% (88-100)
C	5% (2-11)	8% (3-16)	54% (43-64)	39% (28-51)	32% (19-47)	96% (85-99)	24% (13-40)	100% (92-100)
W	15% (9-24)	14% (7-23)	84% (75-91)	59% (48-70)	77% (62-88)	100% (92-100)	76% (60-87)	100% (92-100)
Y	7% (3-14)	6% (2-14)	67% (57-76)	57% (45-68)	60% (44-74)	100% (92-100)	64% (49-78)	100% (92-100)

[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.2 and Table 14.2.1.5

Table 2-4 Secondary Immunogenicity Variable: GMTs and GMRs (95% CI) in Subjects 36 to 59 Months Old for A, C, W, and Y Serogroups

Variable/ Serogroup		1st Vaccination				2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[b]	
		Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 169 (before 2nd)[c]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[d]	Day 358 (21 Days after 2nd)
		ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=101	ACWY PS N=81	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=45	ACWY Ad- N=45
GMT	A	2.06 (2.02-2.1)	2.03 (1.98-2.07)	15 (11-20)	6.82 (4.89-9.53)	2.84 (2.17-3.73)	51 (35-75)	2.51 (1.9-3.32)	149 (99-222)
	C	2.42 (2.22-2.65)	2.54 (2.3-2.8)	7.12 (5.45-9.3)	7.16 (5.31-9.65)	5.06 (3.43-7.46)	129 (83-200)	4.3 (2.89-6.39)	472 (301-739)
	W	3.05 (2.63-3.53)	3.14 (2.66-3.7)	24 (18-31)	12 (8.68-16)	22 (14-33)	371 (256-535)	20 (13-30)	1120 (769-1632)
	Y	2.42 (2.21-2.66)	2.46 (2.21-2.73)	21 (15-29)	14 (9.99-21)	11 (7.14-18)	247 (168-364)	18 (11-29)	911 (613-1353)
GMR	A	NA	NA	7.11 (5.28-9.57)	3.37 (2.41-4.7)	NA	18 (12-26)	NA	59 (40-87)
	C	NA	NA	2.94 (2.27-3.8)	2.82 (2.11-3.76)	NA	25 (17-38)	NA	110 (72-167)
	W	NA	NA	7.78 (5.87-10)	3.78 (2.77-5.18)	NA	17 (12-25)	NA	57 (39-84)
	Y	NA	NA	8.75 (6.38-12)	5.84 (4.09-8.34)	NA	22 (14-32)	NA	50 (33-76)

NA = not applicable
[a] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[c] These values also show persistence 6 months after 1st vaccination.
[d] These values also show persistence 12 months after 1st vaccination.
Source : Table 14.2.1.7 and Table 14.2.1.8

Table 2-5 Percentage of Subjects (95% CI) 12 to 35 Months Old with hSBA Titer ≥ 1:4 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 28 Days after 1st Vaccination[a]			2nd Vaccination 6 Months after 1st Vaccination[a]		2nd Vaccination 12 Months after 1st Vaccination[c]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 29 (before 2nd)	Day 50 (21 Days after 2nd)	Day 358 (12 mo after 2nd)	Day 169 (before 2nd)[d]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[e]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad- N=48	ACWY Ad- N=48	ACWY Ad- N=49	ACWY Ad- N=56	ACWY Ad- N=56	ACWY Ad- N=54	ACWY Ad- N=54
A	0% (0-2)	0% (0-2)	82% (75-87)	70% (63-77)	62% (46-75)	91% (80-98)	29% (17-44)	18% (9-30)	95% (85-99)	9% (3-20)	96% (87-100)
C	5% (2-9)	1% (0-4)	56% (49-63)	49% (42-56)	56% (41-71)	94% (83-99)	73% (59-85)	63% (49-75)	100% (94-100)	33% (21-47)	96% (87-100)
W	8% (4-12)	6% (3-10)	82% (76-87)	80% (73-85)	75% (60-86)	98% (89-100)	87% (74-95)	77% (64-87)	100% (94-100)	54% (40-67)	100% (93-100)
Y	5% (2-8)	3% (1-7)	67% (60-74)	67% (60-74)	60% (44-74)	91% (80-98)	81% (67-91)	67% (53-79)	100% (94-100)	56% (41-70)	100% (93-100)

[a] Subset of PP population receiving 2nd vaccine 28 days after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[c] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[d] These values also show persistence 6 months after 1st vaccination.
[e] These values also show persistence 12 months after 1st vaccination.
Source: Tables 14.2.1.1, 14.2.1.3 and 14.2.1.4

Table 2-6 Percentage of Subjects (95% CI) 12 to 35 Months Old with hSBA Titer ≥ 1:8 for A, C, W, and Y Serogroups

	1st Vaccination				2nd Vaccination 28 Days after 1st Vaccination[a]			2nd Vaccination 6 Months after 1st Vaccination[b]		2nd Vaccination 12 Months after 1st Vaccination[c]	
	Day 1 (Baseline)		Day 29 (28 Days after 1st Vacc.)		Day 29 (before 2nd)	Day 50 (21 Days after 2nd)	Day 358 (12 mo after 2nd)	Day 169 (before 2nd)[d]	Day 190 (21 Days after 2nd)	Day 337 (before 2nd)[e]	Day 358 (21 Days after 2nd)
Serogroup	ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad- N=47	ACWY Ad- N=47	ACWY Ad- N=49	ACWY Ad- N=56	ACWY Ad- N=56	ACWY Ad- N=54	ACWY Ad- N=54
A	0% (0-2)	0% (0-2)	72% (65-78)	61% (53-68)	53% (38-68)	85% (72-94)	23% (12-37)	11% (4-22)	91% (80-97)	7% (2-18)	96% (87-100)
C	3% (1-6)	1% (0.013-3)	47% (40-54)	36% (29-44)	46% (31-61)	90% (77-97)	63% (48-77)	57% (43-70)	100% (94-100)	26% (15-40)	96% (87-100)
W	6% (3-10)	4% (1-7)	72% (65-78)	69% (62-76)	65% (49-78)	90% (77-97)	85% (72-94)	70% (56-81)	100% (94-100)	50% (36-64)	100% (93-100)
Y	4% (2-8)	2% (1-5)	60% (53-67)	57% (50-64)	49% (34-64)	83% (69-92)	71% (56-83)	55% (41-68)	100% (94-100)	46% (32-61)	100% (93-100)

[a] Subset of PP population receiving 2nd vaccine 28 days after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[c] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[d] These values also show persistence 6 months after 1st vaccination.
[e] These values also show persistence 12 months after 1st vaccination.
Source: Tables 14.2.1.2, 14.2.1.5 and 14.2.1.6

Table 2-7 GMTs and GMRs (95% CI) in Subjects 12 to 35 Months Old for A, C, W, and Y Serogroups

		1st Vaccination				2nd Vaccination 28 Days after 1st Vaccination[a]			2nd Vaccination 6 Months after 1st Vaccination[b]		2nd Vaccination 12 Months after 1st Vaccination[c]	
Variable/ Serogroup		**Day 1 (Baseline)**		**Day 29 (28 Days after 1st Vacc.)**		**Day 29 (before 2nd)**	**Day 50 (21 Days after 2nd)**	**Day 358 (12 mo after 2nd)**	**Day 169 (before 2nd)[d]**	**Day 190 (21 Days after 2nd)**	**Day 337 (before 2nd)[e]**	**Day 358 (21 Days after 2nd)**
		ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad+ N=200	ACWY Ad- N=191	ACWY Ad- N=47	ACWY Ad- N=47	ACWY Ad- N=49	ACWY Ad- N=56	ACWY Ad- N=56	ACWY Ad- N=54	ACWY Ad- N=54
GMT	A	2 (1.97-2.03)	2 (1.97-2.03)	18 (15-23)	13 (11-16)	12 (8.98-16)	39 (26-58)	4.15 (3.16-5.45)	2.66 (2.07-3.42)	66 (46-94)	2.41 (1.87-3.12)	168 (116-242)
	C	2.16 (2.03-2.3)	2.05 (1.92-2.18)	7.43 (6.15-8.97)	5.9 (4.87-7.15)	7.81 (5.32-11)	104 (67-161)	18 (12-28)	9.07 (6.35-13)	252 (168-377)	4.79 (3.33-6.88)	575 (381-866)
	W	2.38 (2.14-2.64)	2.26 (2.03-2.52)	17 (14-21)	16 (13-20)	16 (11-25)	61 (42-88)	25 (17-37)	14 (9.6-21)	518 (370-726)	8.19 (5.5-12)	1238 (878-1745)
	Y	2.18 (2.04-2.34)	2.12 (1.98-2.27)	12 (9.39-15)	12 (9.54-15)	10 (6.24-16)	41 (28-60)	19 (12-31)	10 (6.62-16)	302 (211-432)	10 (6.39-16)	915 (633-1322)
GMR	A	NA	NA	9.24 (7.49-11)	6.61 (5.33-8.21)	NA	3.29 (2.27-4.77)	NC	NA	25 (18-35)	NA	70 (49-98)
	C	NA	NA	3.44 (2.87-4.13)	2.88 (2.39-3.47)	NA	13 (8.86-20)	NC	NA	28 (19-40)	NA	120 (82-176)
	W	NA	NA	7.27 (5.95-8.87)	7.09 (5.78-8.7)	NA	3.74 (2.57-5.42)	NC	NA	37 (26-52)	NA	151 (106-215)
	Y	NA	NA	5.4 (4.31-6.75)	5.69 (4.51-7.16)	NA	4.05 (2.71-6.04)	NC	NA	29 (20-43)	NA	91 (62-133)

[a] Subset of PP population receiving 2nd vaccine 28 days after 1st vaccination.
[b] Subset of PP population receiving 2nd vaccine 6 months after 1st vaccination.
[c] Subset of PP population receiving 2nd vaccine 12 months after 1st vaccination.
[d] These values also show persistence 6 months after 1st vaccination.
[e] These values also show persistence 12 months after 1st vaccination.
Source: Table 14.2.1.7, 14.2.1.8 and 14.2.1.9

Table 2-8 Number (%) of Subjects with Solicited AEs (Reactions) Between Days 1 to 7 by Age Stratum and by Vaccination

Type of AE	12 – 35 Months Old				36 – 59 Months Old			
	1st Vaccination		2nd Vaccination		1st Vaccination		2nd Vaccination	
	ACWY Ad+ N=205	ACWY Ad- N=206	ACWY Ad+ N=200	ACWY Ad- N=201	ACWY Ad- N=125	ACWY PS N=81	ACWY Ad- N=120	ACWY Ad-[a] N=74
Any Reaction	115 (56%)	127 (62%)	98 (49%)	103 (51%)	78 (62%)	48 (59%)	62 (52%)	32 (43%)
Local Reaction	78 (38%)	90 (44%)	75 (38%)	70 (35%)	56 (45%)	43 (53%)	45 (38%)	26 (35%)
Systemic Reaction	63 (31%)	78 (38%)	62 (31%)	61 (30%)	36 (29%)	21 (26%)	34 (28%)	10 (14%)
Other Reaction	26 (13%)	27 (13%)	22 (11%)	13 (6%)	13 (10%)	8 (10%)	11 (9%)	4 (5%)

[a] Subjects receiving MenACWY PS at 1st vaccination
Source: Table 14.3.1.1.2.1

Table 2-9 Number (%) of Subjects with Unsolicited AEs by Age Stratum, for any Vaccination, Twenty-Eight Days After the First Vaccination and Twenty-One Days After the Second Vaccination

Type of AE		**12 – 35 Months Old**		**36 – 59 Months Old**	
		ACWY Ad+ N=205	**ACWY Ad- N=206**	**ACWY Ad- N=125**	**ACWY PS / ACWY Ad-[a] N=81**
Any AE	Any Vaccination	117 (57%)	99 (48%)	64 (51%)	41 (51%)
	1st Vaccination	78 (38%)	65 (32%)	41 (33%)	26 (32%)
	2nd Vaccination	40 (20%)	33 (16%)	23 (19%)	15 (20%)
Possibly / probably related AE	Any Vaccination	9 (4%)	9 (4%)	3 (2%)	1 (1%)
	1st Vaccination	6 (3%)	4 (2%)	1 (1%)	0
	2nd Vaccination	6 (3%)	5 (2%)	2 (2%)	1 (1%)
SAE	Any Vaccination	13 (6%)	12 (6%)	11 (9%)	9 (11%)
	1st Vaccination	2 (1%)	1 (<1%)	0	0
	2nd Vaccination	2 (1%)	1 (<1%)	1 (1%)	0
AE leading to discontinuation	Any Vaccination	3 (1%)	1 (<1%)	0	0
	1st Vaccination	0	0	0	0
	2nd Vaccination	0	0	0	0
Possibly / probably related SAE	Any Vaccination	0	0	0	0
Death	Any Vaccination	0	0	0	0

[a] Recipients of ACWY PS at 1st vaccination were administered MenACWY without adjuvant at 2nd vaccination
Source: Table 14.3.1.1.11, Table 14.3.1.1.11.3, Table 14.3.1.1.11.4, Table 14.3.1.1.14, Table 14.3.1.1.14.1., Table 14.3.1.1.14.2, Table 14.3.1.1.14.3, Table 14.3.1.1.14.4, Table 14.3.1.1.7, Table 14.3.1.1.7.1, Table 14.3.1.1.7.2, Table 14.3.1.1.8, Appendix 16.2.7.5

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics Inc. 4560 Horton Street Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P8**	

Title of study: A Phase 2, Randomized, Single-blind, Controlled, Single-Center Study to Compare the Safety and Immunogenicity of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune™ *) Administered to Healthy Children 2-10 Years of Age and an Open-label Study to Assess the Safety and Immunogenicity of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine Administered to Healthy Toddlers 12-23 Months of Age

Protocol number: V59P8

Investigators: Nicola Klein, MD (who replaced Steven Black, MD, who retired from Kaiser)

Study centers: Kaiser Permanente Vaccine Study Center, One Kaiser Plaza, Ordway Building, 16th Floor, Oakland, CA 94612

Publication (reference): None

Study period: 14 APR 05 to 03 NOV 06	**Phase of development:** Phase 2

Objectives:

Primary Objective:

1. To compare the immunogenicity of a single dose of Novartis MenACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as percentage of subjects with serum bactericidal activity (i.e., hSBA ≥ 1:4) directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** after vaccination, when administered to healthy children 2 to 10 years of age.

Secondary Objectives:

1. To compare the immunogenicity of a single dose of Novartis MenACWY Conjugate

* Menomune™ is a registered trademark of Sanofi Pasteur Inc. (formerly Aventis Pasteur).

Name of Sponsor Novartis Vaccines and Diagnostics Inc. 4560 Horton Street Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P8**	

Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as hSBA geometric mean titer (GMT) antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** after vaccination, when administered to healthy children 2 to 10 years of age.

2. To compare the immunogenicity of a single dose of Novartis MenACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as: (a) percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y; and (b). hSBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** after vaccination, when administered to the following groups of healthy children: 2 to 5 years of age and 6 to 10 years of age.
3. To compare the immunogenicity of a single dose of Novartis MenACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune), defined as: (a) percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y; and (b) hSBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** and at **12 months** after vaccination, when administered to healthy toddlers 12 to 23 months of age (who received Novartis MenACWY Conjugate Vaccine) and healthy children 3 to 5 years of age (who received Menomune).
4. To compare the immunogenicity of a single dose of Novartis MenACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide (PS) vaccine (Menomune), defined as: (a) percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y; and (b) hSBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **12 months** after vaccination, when administered to healthy children 2 to 10 years of age, overall and within the following age groups: 2 to 5 years of age and 6 to 10 years of age.

Name of Sponsor Novartis Vaccines and Diagnostics Inc. 4560 Horton Street Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine	VOLUME: PAGE:	
Name of Active Ingredient Men A-CRM_{197} conjugate, Men C-CRM_{197} conjugate, Men W-135-CRM_{197} conjugate, Men Y-CRM_{197} conjugate	**Study number: V59P8**	

Safety Objectives:

1. To assess the safety and tolerability of a single dose of the Novartis MenACWY Conjugate Vaccine compared to the safety and tolerability of a single dose of Menomune when administered to healthy children 2 to 10 years of age.
2. To assess the safety and tolerability of a single dose of the Novartis MenACWY Conjugate Vaccine when administered alone or concomitant with PnC to healthy toddlers 12 to 15 months of age and when administered alone or concomitant with DTaP to healthy toddlers 16 to 23 months of age.

Methodology: This trial was designed as a phase 2, single-center study divided in two parts: the first part was randomized, single-blind, and controlled to evaluate the safety and immune response at 1 and 12 months following vaccination with one dose of either Novartis MenACWY Conjugate Vaccine or Menomune in healthy children 2 to 10 years of age; the second part was open label with and without concomitant PnC (for toddlers 12 to 15 months of age), or with and without concomitant DTaP (for toddlers 16 to 23 months of age) to evaluate the safety and immune response at one and twelve months following vaccination with one dose of Novartis MenACWY Conjugate Vaccine in healthy toddlers 12 to 23 months of age.

Part 1: Healthy children 2 to 10 years of age were randomly assigned to one of two groups (Novartis MenACWY Conjugate Vaccine or Menomune) in a 1:1 ratio. The randomization was stratified by age with the following targets per age strata: children 2 to 5 years of age (n = 350), and children 6 to 10 years of age (n = 350).

Vaccine Age	Novartis MenACWY Conjugate Vaccine (n = 350)	Menomune (n = 350)
2-5 years (= 2 to <6 years) (n = 350)	175	175
6-10 years (= 6 to <11 years) (n = 350)	175	175

Part 2: Healthy toddlers 12 to 23 months of age were randomly assigned to one of two groups (Novartis MenACWY Conjugate Vaccine alone or with concomitant PnC for toddlers 12 to 15 months of age; and alone or with concomitant DTaP for toddlers 16 to 23 months of age) in a 1:1 ratio. The randomization was stratified by age with the following targets per age strata: toddlers 12 to 15 months of age (n = 150), and toddlers

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16 to 23 months of age (n = 150). Additionally, as Menomune is not licensed in the US in children under 2 years of age, during Part 2, a subset of one hundred 3- to 5-year-old children drawn from the Part 1 two- to five-year-old age stratum in the Menomune control group served as immunogenicity controls for toddlers aged 12 to 23 months in Part 2.

Vaccine / Age	Novartis MenACWY Conjugate Vaccine Alone	Novartis MenACWY Conjugate Vaccine with PnC	Novartis MenACWY Conjugate Vaccine with DTaP
12-15 months (= 12 to <16 months) (n = 150)	75	75	
16-23 months (= 16 to <24 months) (n = 150)	75		75

Number of subjects (planned and analyzed): 700 healthy children 2 to 10 years of age and 300 healthy toddlers 12 to 23 months of age were planned. Of the 619 children randomized, 618 subjects were treated; of the 291 toddlers randomized, 289 were treated.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria (healthy children 2 to 10 years)

Individuals eligible for enrollment in this study were male and female children, who were:

1. 2 to 10 years of age inclusive (and who gave written assent, if applicable) whose parent or legal guardian gave written informed consent at the time of enrollment;
2. available for all visits and telephone calls scheduled for the study;
3. in good health as determined by:
   - medical history;
   - physical assessment;
   - clinical judgment of the investigator.

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Exclusion Criteria (Healthy children 2 to 10 years)

Individuals not eligible to be enrolled in the study were those:

1. whose parent or legal guardian was unwilling or unable to give written informed consent to participate in the study (or who was unwilling or unable to give written informed assent, if applicable);
2. whose parent or legal guardian was perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* serogroup A, C, W, and/or Y infection within 60 days prior to enrollment;
5. who had previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of OMP-containing Hib vaccines was permitted (e.g., Comvax, PedvaxHIB);
6. who had received any investigational agents or vaccines within the 90 days prior to enrollment or who expected to receive an investigational agent or vaccine prior to the completion of the study;
7. who had received any licensed vaccines within 1 month prior to enrollment or for whom receipt of a licensed vaccine was anticipated within 1 month after vaccination (Exception: Influenza vaccine could be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination) NOTE: Concomitant administration of licensed vaccines was permitted on the day of study enrollment;
8. who had received a live viral vaccine within 60 days prior to enrollment;
9. who had experienced within 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment, or antiviral therapy) or had experienced fever (≥ 38°C [≥ 100.4°F]) within the previous 3 days to study entry;
10. who had any serious acute, chronic, or progressive disease (e.g., any history of neoplasm, cancer, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: Subjects with mild asthma were eligible for enrollment.

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Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids were not eligible for enrollment);

11. who had epilepsy or any progressive neurological disease;
12. who had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
13. who had a known or suspected impairment/alteration of immune function, either congenital, acquired, or resulting from (for example):
    - receipt of immunosuppressive therapy within the past 30 days (any systemic corticosteroid administered for more than 5 days, or, in a daily dose, > 1 mg/kg/day prednisone or equivalent during any of the previous 30 days, or cancer chemotherapy);
    - receipt of immunostimulants;
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within the past 90 days and for the full length of the study;
14. who had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (Exception: subjects who had received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.] could have been enrolled 7 days after the last dose);
15. who were known to have a bleeding diathesis or any condition that could be associated with a prolonged bleeding time;
16. who had Down's syndrome or other known cytogenic disorders;
17. whose families were planning to leave the area of the study site before the end of the study period;
18. who had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Inclusion Criteria (healthy toddlers 12 to 23 months of age)

Individuals eligible for enrollment in this study were male and female toddlers who were:

1. 12 to 23 months of age inclusive whose parent or legal guardian had given written informed consent at the time of enrollment;
2. available for all visits and telephone calls scheduled for the study;

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3. in good health as determined by:
   - medical history;
   - physical assessment;
   - clinical judgment of the investigator;
4. up to date with age-appropriate immunizations for diphtheria, tetanus, pertussis, polio, hepatitis B, *Haemophilus influenzae* type b, and pneumococcus as noted in the following table:

Vaccine	**# of Immunizations Required Prior to Enrollment (12-15 months of age)**	**# of Immunizations Required Prior to Enrollment (16-23 months of age)**
Diphtheria, tetanus, acellular pertussis (DTaP)	3 doses	3 doses
Inactivated polio virus (IPV)	2 doses	2 doses
Hepatitis B	2 doses	2 doses
H influenzae type b (Hib)	2[a] or 3 doses	3[b] or 4 doses
Pneumococcal conjugate vaccine (PnC)	2 doses	3 doses

[a] Hib, at least 2 doses if both were PRP-OMPC
[b] Hib, at least 3 doses if at least 2 doses were PRP-OMPC

Exclusion Criteria (healthy toddlers 12 to 23 months of age)

Individuals not eligible to be enrolled in the study were those:

1. whose parent or legal guardian was unwilling or unable to give written informed consent to participate in the study;
2. whose parent or legal guardian was perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* serogroup A, C, W, and/or Y infection within 60 days prior to enrollment;
5. who had previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of OMP-containing Hib vaccines was permitted (e.g., Comvax, PedvaxHIB);

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6. who had received any investigational agents or vaccines within the 90 days prior to enrollment or who expected to receive an investigational agent or vaccine prior to the completion of the study;
7. who had received any licensed vaccines within 1 month prior to enrollment or for whom receipt of a licensed vaccine was anticipated within 1 month after vaccination (Exception: Influenza vaccine could be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination);
8. who had received a live viral vaccine within the previous 60 days;
9. who had experienced within the previous 7 days significant acute or chronic infection (for example requiring systemic antibiotic vaccine or antiviral therapy) or had experienced fever (≥ 38°C [≥ 100.4°F]) within the previous 3 days to study entry;
10. who had any serious acute, chronic, or progressive disease (e.g., any history of neoplasm, cancer, insulin-dependent diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: Subjects with mild asthma were eligible for enrollment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids were not eligible for enrollment);
11. who had epilepsy or any progressive neurological disease;
12. who had a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
13. who had a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within the past 30 days (any systemic corticosteroid administered for more than 5 days, or, in a daily dose > 1 mg/kg/day, prednisone or equivalent during any of the previous 30 days, or cancer chemotherapy);
    - receipt of immunostimulants;
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within the past 90 days and for the full length of the study;

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14. who had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (Exception: subjects who had received an oral or parenteral β-lactam antibiotic (examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.) could be enrolled 7 days following the last dose);
15. who were known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
16. who had Down's syndrome or other known cytogenic disorders;
17. whose families were planning to leave the area of the study site before the end of the study period;
18. who had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

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Test product, dose, mode of administration, lot number:

Single dose injection, IM (left deltoid)

The investigational Novartis MenACWY Conjugate Vaccine was obtained by extemporaneous mixing of the lyophilized Men A component to be resuspended with the Men CWY liquid component. The vaccine was to be prepared just prior to administration to the study subject.

After reconstitution, Novartis MenACWY Conjugate Vaccine had the following composition per 0.5 mL of injectable suspension (see following table):

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	
WFI	

CRM = cross-reactive material

The following lot numbers were used in the study:

Meningococcal serogroup A conjugate components: lot 002011;

Meninogococcal serogroup CWY conjugate components: lot U79P33D1.

Duration of study: Each subject participated for 12 months in the study. Each subject received a single injection of study vaccine on day 1 and returned to the clinic after 1 and 12 months for postvaccination assessments.

Reference therapy, dose, mode of administration, lot number: Menomune

Single dose injection, SC (left upper arm)

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Menomune (manufactured by Aventis Pasteur Inc., Swiftwater, PA; lot numbers UE345AA and UE268AA; expiration dates 12Jul06 and 20Feb09, respectively) was supplied as a single dose (one vial of vaccine and one vial of diluent). The vaccine consisted of four meningococcal capsular polysaccharide serogroups (A, C, W-135, and Y). After reconstitution with the liquid diluent, Menomune had the following composition per 0.5 mL of injectable solution:

Composition	Quantity
Isolated product from each of groups A, C, W-135, and Y	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: WFI	Qs to 0.5 mL

Criteria for Evaluation:

Immunogenicity

Serum bactericidal activity (SBA) was measured for each serogroup in the presence of human complement (hSBA) and then expressed as GMT and percentage of subjects with hSBA titer ≥ 1:4 (% ≥ 1:4) and ≥ 1:8 (% ≥ 1:8).

Safety

Measures of safety and reactogenicity included data from observed local reactions (e.g., toddlers 12 to 23 months of age: tenderness, erythema, and induration; children 2 to 10 years of age: pain, erythema, and induration) and systemic reactions (e.g., toddlers 12 to 23 months of age: change in eating habits, sleepiness, persistent crying lasting more than 3 hours, irritability, vomiting, and diarrhea; children 2 to 5 years of age: change in eating habits, sleepiness, irritability, vomiting, diarrhea, arthralgia, and headache; children 6 to 10 years of age: chills, nausea, malaise, myalgia, arthralgia, and headache).

In addition axillary (toddlers aged 12 to 23 months, children 2 to 5 years) or oral (children aged 6 to 10 years) temperature and analgesic or antipyretic medication use were documented. Local, systemic, or other reactions and all other adverse events were collected during the first 7 days after the injection, including the day of vaccination (study days 1 through 7). Serious adverse events (SAE) and/or adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

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Statistical Methods:

Immunogenicity

The primary immunogenicity objective was to compare the percentage of responders (defined as the percentage of subjects with hSBA titers ≥ 1:4) in children aged 2 to 10 years at 1 month after immunization with Chiron MenACWY versus Menomune against each of the four serogroup components. Other comparisons of interest included comparing percentage of responders in the subgroups of children aged 2 to 5 and 6 to 10 years. These comparisons were also performed using the responder criterion hSBA titers ≥ 1:8 and for hSBA GMTs.

The percentage of responders against each of the four serogroup components (defined as the percentage of subjects with hSBA titers ≥ 1:4) in toddlers aged 12 to 23 months was compared after immunization with Novartis MenACWY alone or in combination with PnC or DTaP for toddlers aged 12 to 15 and 16 to 23 months, respectively. These comparisons were also performed using the responder criterion hSBA titers ≥ 1:8 and for hSBA GMTs.

Safety

All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 9.1, and grouped by MedDRA preferred terms into frequency tables according to MedDRA system-organ-class categories.

Interim Analysis

To facilitate the planning of future trials, a group-unblinded interim analysis was performed before all subjects had completed visit 2, to assess immunogenicity and 1-month safety (including local and systemic postimmunization reactions within 7 days after immunization). The analysis was conducted with data from 504 subjects for safety (316 subjects 2 to 10 years of age; 188 subjects 12 to 23 months of age) and 302 subjects for immunogenicity (211 subjects 2 to 10 years of age; 91 subjects 12 to 23 months of age). The results of this analysis did not alter the course of the trial. The analysis was governed by the procedures specified in the Novartis Biostatistics & Statistical Reporting (B&SR) document entitled "Interim Analysis in a Clinical Trial."

Summary and Conclusions:

In **part 1** of the study, 619 children aged 2 to 10 years were enrolled and randomly assigned by age group (2- to 5-year-old and 6- to 10-year-old subjects) to MenACWY

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Conjugate Vaccine or the reference compound Menomune. Of the 305 children aged 2 to 5 years, 152 subjects were randomized to receive MenACWY, and 153 were randomized to receive Menomune. Of the 314 children aged 6 to 10 years, 157 subjects were randomized to each vaccine group (MenACWY or Menomune). Demographic characteristics were similar among the randomized groups.

Six hundred eighteen (618) children were vaccinated. The parents or legal guardian of one subject (in the ACWY 2-5 group) signed the informed consent form but withdrew the subject from participation prior to vaccination.

Five hundred twenty-five (525) subjects completed the protocol, including 84%, 82%, 87%, and 85% of the MenACWY 2-5, Menomune 2-5, MenACWY 6-10, and Menomune 6-10 subjects, respectively. Among the 94 subjects who did not complete the study, none of the subjects was withdrawn due to local or systemic reactions or due to AEs. Twenty subjects withdrew consent, 24 subjects were lost to follow-up, 46 subjects were withdrawn due to administrative reasons, 1 subject was withdrawn due to a protocol deviation, and 3 subjects were withdrawn for a reason that could not be classified according to the study protocol (not able to keep the appointment).

The following number of children aged 2 to 10 years were included in the analysis datasets:

Data Set	**MenACWY 2-5**	**Menomune 2-5**	**MenACWY 6-10**	**Menomune 6-10**
No. of Subjects Randomized	**152**	**153**	**157**	**157**
Safety	151 (99%)	153 (100%)	157 (100%)	157 (100%)
Modified Intention-to-Treat	138 (91%)	147 (96%)	148 (94%)	152 (97%)
Per Protocol – 1-Month Analysis	136 (89%)	140 (92%)	148 (94%)	145 (92%)
Per Protocol - Persistence	121 (80%)	116 (76%)	135 (86%)	126 (80%)

In **part 2** of the study, 291 toddlers aged 12 to 23 months were enrolled and randomized to MenACWY vaccine alone or together with PnC vaccination (toddlers 12 to 15 months of age) or DTaP vaccination (toddlers 16 to 23 months of age). Of the 147

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toddlers aged 12 to 15 months, 74 subjects were randomized to receive MenACWY alone, and 73 subjects were randomized to receive MenACWY+PnC. Of the 144 toddlers aged 16 to 23 months, 71 subjects were randomized to receive MenACWY alone, and 73 subjects were randomized to receive MenACWY+DTaP. Demographic characteristics were similar among the randomized groups. Additionally, 100 healthy children aged 3 to 5 years, who had received Menomune in part 1 of the study, were used as controls for the 12- to 23-month-old part 2 toddlers.

Two hundred eighty-nine (289) toddlers were vaccinated. The parents or legal guardian of two subjects (both in the MenACWY+PnC group) signed the informed consent form but withdrew the subjects from participation prior to vaccination.

Two hundred thirty-six (236) subjects completed the protocol, including 84%, 82%, 83%, and 75% of the MenACWY 12-15, MenACWY+PnC, MenACWY 16-23, and MenACWY+DTaP subjects, respectively. Among the 55 subjects who did not complete the study, none of the subjects was withdrawn due to local or systemic reactions or due to AEs. Seventeen subjects withdrew consent, 15 subjects were lost to follow-up, and 23 subjects were withdrawn due to administrative reasons.

The following number of toddlers aged 12 to 23 months were included in the datasets:

Data Set	MenACWY 12-15	MenACWY+PnC	MenACWY 16-23	MenACWY+DTaP
No. of Subjects Randomized	74	73	71	73
Safety	74 (100%)	71 (97%)	71 (100%)	73 (100%)
Modified Intention-to-Treat	62 (84%)	62 (85%)	66 (93%)	64 (88%)
Per Protocol - 1 Month Analysis	61 (82%)	61 (84%)	62 (87%)	62 (85%)

Immunogenicity

Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at One Month After Vaccination of Children 2 to 10 Years of Age

The primary immunogenicity analysis compared the percentage of subjects with hSBA titers ≥ 1:4 among the children 2 to 10 years of age at approximately 1 month following

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immunization with either MenACWY or Menomune. At 1 month after vaccination, the percentage of subjects with hSBA titers ≥ 1:4 was higher in the MenACWY group than in the Menomune group (81% to 94% for MenACWY against the four serogroups and 44% to 72% for Menomune). The differences between the MenACWY and the Menomune vaccination groups were 37%, 19%, 23%, and 31% for serogroups A, C, W, and Y, respectively. The lower limit of the 95% CIs for the difference at 1 month after vaccination of the four serogroups were all greater than 0%, indicating a superiority of MenACWY over Menomune based on a criterion of the percentage of subjects who had hSBA titers ≥ 1:4.

The increase in GMT after vaccination was more pronounced in the MenACWY group than in the Menomune group. MenACWY exhibited 8.6- to 18-fold increases from baseline in 1 month GMTs, while Menomune produced 2.5- to 4.6-fold increases from baseline in 1 month GMTs. The differences between the vaccine groups were statistically significant for all four serogroups ($P < .001$ for all serogroups).

Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at One Month After Vaccination of Children 2 to 5 Years and 6 to 10 Years of Age

Overall, the results of the subgroups for the percentage of subjects with an hSBA titer ≥ 1:4 were similar to those of the whole 2- to 10-year population. Especially for serogroup A, no differences were observed between the whole population and the subgroups. Slight differences were seen for the serogroups W and Y, where the difference between MenACWY and Menomune was higher in the younger children (aged 2 to 5 years, difference 35% and 38%, respectively) than in the older children (aged 6 to 10 years, difference 10% and 25%, respectively), but the lower limit of the 95% CIs was always greater than 0%, indicating statistically significant higher responder rates in the MenACWY groups. For serogroup C, the difference between MenACWY and Menomune was 31% for children aged 2 to 5 years (95% CI: 20%-42%), but only 6% for children between 6 to 10 years (95% CI: –2%-15%).

Generally, the increases in GMT after vaccination were higher in the 6- to 10-year subgroup than in the 2- to 5-year subgroup. Comparing the GMT increases after MenACWY and Menomune, higher increases were observed after MenACWY than after Menomune for both subgroups and for all serogroups. For the children aged 2 to 5 years, the GMTs at 1 month postvaccination ranged from 14 to 43 after MenACWY and from 5.8 to 7.84 after Menomune. The corresponding GMTs were 45 to 80 for

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MenACWY and 6.84 to 33 after Menomune for the children aged 6 to 10 years.

Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at One Month After Vaccination of Toddlers 12 to 23 Months of Age and Children 3 to 5 Years of Age

At 1 month after vaccination, 81% to 90% of the toddlers receiving MenACWY had an hSBA titer ≥ 1:4 for serogroups A, C and W and 64% were responders with respect to serogroup Y. In comparison, 42% to 63% of the children aged 3 to 5 years who received Menomune were responders to serogroups A, C, W, and Y (51% for serogroup Y). The lower limits of the 95% CIs for the 1-month difference between the two vaccines for each serogroup were greater than 0%, indicating a superiority of ACWY immunogenicity over Menomune.

At 1 month after vaccination, GMTs for all serogroups were higher in toddlers who had received MenACWY than in 3- to 5-year-old children of the Menomune group (Table 11.4.1.2.3-1). After MenACWY vaccination, the 1-month GMTs were 11 to 22, and after Menomune vaccination, 7.09 to 9.52. The differences between the two groups were statistically significant except for the Y serogroup ($P < .001$ for serogroups A, C, and W, and $P = .20$ for serogroup Y).

Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at 12 Months After Vaccination of Children 2 to 10 Years of Age

Twelve months after vaccination, the percentage of responders (subjects with hSBA ≥ 1:4) was again statistically significantly higher in the MenACWY group than in the Menomune group (lower limits of all 95% CIs for the differences between the two vaccine groups were greater than 0%). The decrease in the responder rate from 1 to 12 months was most pronounced for serogroup A (from 82% to 28% responders at 1 and 12 months after MenACWY and from 45% to 18% responders after vaccination with Menomune). Rather similar responders rates were observed at 1 and 12 months after vaccination for serogroups W and Y after MenACWY vaccination. The differences between MenACWY and Menomune always resulted in lower limits of the 95% CIs greater than 0%, indicating superiority of ACWY over Menomune.

GMTs decreased from 1 month to 12 months after vaccination, but remained higher after MenACWY than after Menomune (except for serogroup C, $P = .27$).

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Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at 12 Months After Vaccination of Children 2 to 5 Years and 6 to 10 Years of Age

Regarding the percentage of responders at 12 months after vaccination for the subgroups of children aged 2 to 5 years and 6 to10 years, some minor differences from the whole population were observed.

For children aged 2 to 5 years, the differences between the MenACWY and the Menomune groups showed a superiority of MenACWY with lower limits of the 95% CIs greater than 0% for serogroups C, W, and Y; a 95% CI of 0-19% was noted for serogroup A.

For children aged 6-10 years, the differences in responder rates between the two vaccines at 12 months after vaccination showed superiority of MenACWY over Menomune for the serogroups W and C, but not for serogroups A and C (95% CI of –2% –20% and –7% to 15%, respectively). Since the CIs were entirely to the right of -10%, noninferiority of MenACWY to Menomune may be concluded.

Percentage of Responders (hSBA ≥ 1:8) in Children 2 to 10 Years of Age

The percentages of responders defined using hSBA titers ≥ 1:8 as criterion (at 1 month: 73% to 92% for MenACWY and 37% to 66% for Menomune) were slightly lower than the percentages of responders using the hSBA titers ≥ 1:4, but the differences between the MenACWY and Menomune groups were similar for both criteria.

Percentage of Responders (hSBA ≥ 1:4) and hSBA GMT at One Month After Vaccination of Toddlers of 12 to 15 Months and 16 to 23 Months of Age

The groups of toddlers aged 12 to 15 months, who received either MenACWY alone or in combination with PnC and the groups of toddlers aged 16 to 23 months, who received MenACWY alone or in combination with DTaP were compared. Some differences were seen for serogroup Y, where the number of responders among the toddlers aged 16 to 23 months was higher than the younger toddlers: at 1 month, 76% and 77% (MenACWY alone and +DTaP, respectively) of the toddlers aged 16 to 23 months were responders compared to 53% and 52% (MenACWY alone and +PnC) of the toddlers aged 12 to 15 months. Concomitant vaccination with PnC (toddlers aged 12 to 15 months) or DTaP (toddlers aged 16 to 23 months) had no remarkable influence on the number of responders at 1 month after vaccination. The only differences were seen for serogroup A, where the number of responders was higher after vaccination with

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MenACWY+PnC compared to MenACWY alone (85% and 67%, respectively), and serogroup W, where the number of responders was again higher in the group receiving combined vaccination (97% responders after MenACWY+DTaP and 84% responders after MenACWY alone).

GMT results for the different subgroups were similar to those of the whole group of toddlers, except for the toddlers, aged 12 to 15 months, who received MenACWY alone. For this group the GMT increase from baseline to 1 month after vaccination was lower in serogroup A and Y compared to toddlers aged 16 to 23 months, but no noteworthy differences were seen between toddlers receiving MenACWY alone or combined with PnC or DTaP. Concomitant vaccination with PnC (toddlers aged 12-15 months) or DTaP (toddlers aged 16-23 months) had no remarkable influence on the increase in GMT from pre-vaccination to 1 month after vaccination. All *P* values for the comparisons were > .05, except for the comparison MenACWY alone / MenACWY+DTaP for serogroup W: a 7.6-fold increase was observed after vaccination with ACWY alone, whereas a 12-fold increase was observed after vaccination with MenACWY+DTaP ($P = .031$).

Percentage of Responders (hSBA ≥ 1:8) in Toddlers of 12 to 23 Months of Age

When comparing these results for the responder criterion hSBA titer ≥ 1:8 with those obtained with the criterion hSBA titer ≥ 1:4, only marginal differences were observed: the number of responders was only slightly lower than for the 1:4 criterion (75% to 87% for serogroups A, C and W and 51% for serogroup Y), and there were no statistically significant differences between MenACWY alone and MenACWY+PnC or MenACWY+DTaP.

Safety

Children Aged 2 to 10 Years

In children 2 to 5 years of age, 56% of the children in the MenACWY group and 44% in the Menomune group experienced at least one local, systemic, or other reaction during the 7-day reactogenicity monitoring period. In children 6 to 10 years of age, the respective percentages were 55% in the MenACWY group and 43% in the Menomune group.

Injection site reactions were observed in 37% of the 2- to 5-year-old children in the MenACWY group and in 24% of the children in the Menomune group. In children 6 to

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10 years of age injection site reactions were observed in 45% of the children after vaccination with MenACWY and in 32% of the children after Menomune.

In children 2 to 5 years of age, 36% of the children in the MenACWY group and 29% of the children in the Menomune group experienced systemic reactions. In children 6 to 10 years of age the respective percentages were 25% in the MenACWY group and 18% in the Menomune group.

Other reactions were observed in 26% and 20% of the children aged 2 to 5 years after vaccination with MenACWY and Menomune, respectively, and in 24% and 15% of children 6 to 10 years of age.

Overall, the percentage of subjects with local, systemic, or other reactions was higher in the MenACWY groups than in the Menomune groups; particularly, local reactions were observed more often after vaccination with MenACWY than after Menomune. Most reactions were mild and of limited duration with no more than 2% of subjects in either group reporting severe reactions. The differences between the vaccine groups were most pronounced for erythema and induration, where more than twice as many subjects reported these symptoms after MenACWY.

The time of first onset of local or systemic reactions was mainly within 3 days after vaccination, and no differences in time of first onset were apparent between vaccination groups.

Change in eating habits, sleepiness, and irritability were the most frequently reported systemic reactions in children aged 2 to 5 years. There was no apparent difference in systemic reaction incidence and onset between the MenACWY and the Menomune group. In children aged 6 to 10 years, the incidence of chills, myalgia (both reported by 8% of the subjects after MenACWY and 3% after Menomune), and headache was slightly higher in the MenACWY group than in the Menomune group. All other symptoms of systemic reaction were less frequently reported, were more evenly distributed, and, in more than 50% of the subjects, were observed within the first 3 days after vaccination.

The frequency of use of analgesic/antipyretic medication was higher in the MenACWY groups (overall and between days 1 to 3 and 4 to 7). There were no apparent differences between the vaccination groups in the percentage of subjects who stayed at home due to reactions or the percentage of subjects with oral temperature ≥ 38°C.

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Local reactions of erythema and/or induration ≥ 100 mm were observed in three subjects in the MenACWY 6-10 group. All three subjects showed no noteworthy systemic reactions.

Toddlers Aged 12 to 23 Months

Among the groups of toddlers receiving MenACWY alone or together with PnC or DTaP vaccination, 85% to 89% of the subjects experienced at least one local, systemic, or other reaction during the 7-day reactogenicity monitoring period. Injection site reactions were observed in 41% to 56% of subjects in the MenACWY groups and in 5% of subjects in the Menomune group, systemic reactions were reported for 64% to 72% in the MenACWY groups and for 22% in the Menomune group, and other reactions were reported for 35% to 62% of the subjects in the toddler groups and for 13% of the children aged 3 to 5 after vaccination with Menomune.

There was no indication that the concomitant vaccination with PnC or DTaP increased the number of subjects who showed any local, systemic, or other reactions.

The time of first onset of local or systemic reactions was mainly within 3 days after vaccination and no differences in time of first onset were apparent between vaccination groups. In most cases local reactions were already resolved by day 3.

Local reactions were mainly mild in intensity. Combined vaccination of MenACWY with PnC or DTaP did not increase the intensity of local reactions.

Change in eating habits, sleepiness, and irritability were the most frequently reported systemic reactions in toddlers aged 12 to 23 months. Change in eating habit was slightly more frequently reported after combined vaccination (15%, 29%, 18% and 25% for the MenACWY 12-15, MenACWY+PnC, MenACWY 16-23, and MenACWY+DTaP groups, respectively). The incidence of the other symptoms gave no indication of a difference between MenACWY alone and combined vaccination.

The frequency of use of analgesic/antipyretic medication was higher in the combined vaccination groups (overall and when regarding days 1 to 3 and 4 to 7 separately [except for the toddlers aged 12 to 15 months]), but this was mainly due to a high number of toddlers in the combined vaccination groups who received analgesic/antipyretic medication in advance to prevent reactions (35% and 29% in the MenACWY+PnC and MenACWY+DTaP groups compared to 19% and 11% in the MenACWY alone groups). There were no apparent differences between the vaccinations groups in the percentage of

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subjects with temperature ≥ 38°C.

Other Adverse Events

There were no deaths reported during or after the study. Three children aged 2 to 10 years (two children in the MenACWY 2-5 group and one child in the Menomune 2-5 group) and 10 toddlers aged 12 to 23 months (two toddlers in both the MenACWY 12-15 and MenACWY+DTaP groups and three toddlers in both the MenACWY+PnC and MenACWY 16-23 groups) experienced SAEs during the study. None of the SAEs was considered related to a study vaccine by the investigator.

Six of 151 (4%) and 15 of 157 (10%) of children in the MenACWY 2-5 and MenACWY 6-10 groups, respectively, and 7 of 153 (5%) and 9 of 157 (6%) children in the Menomune 2-5 and Menomune 6-10 groups, experienced AEs that were considered by the investigator to be possibly or probably related to study vaccines. Irritability, dizziness, headache, and pruritus were the only vaccine-related AEs reported for more than one subject within a vaccine group. Except for viral infection (MenACWY 2-5) and alopecia areata (Menomune 2-5), all these events occurred within the first 7 days after vaccination. Abdominal pain reported by one subject in the MenACWY 6-10 group and chills, malaise, and myalgia reported by one subject in the Menomune 6-10 group were of severe intensity; all other vaccine-related AEs were mild to moderate in intensity.

Six of 74 (8%) and one of 71 (1%) MenACWY toddlers who received MenACWY alone and one of 71 (1%) and four of 73 (5%) toddlers who received combined vaccination experienced AEs that were considered by the investigator to be possibly or probably related to study vaccines. Diarrhea and irritability were the only vaccine-related AEs reported for at least two MenACWY subjects; somnolence and eating disorders were the only AEs reported for at least two Menomune subjects. Except for irritability, decreased appetite, and somnolence observed in subjects in the MenACWY 12-15 group, and alopecia (in a Menomune subject), all events occurred within the first 7 days after vaccination. Only urticaria reported by one subject in the MenACWY+DTaP group was of severe intensity; all other related AEs were of mild to moderate in intensity.

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Conclusions

1. Children Aged 2 to 10 Years

- As assessed by either the percentage of subjects with hSBA ≥ 1:4 or GMTs directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination Novartis MenACWY Conjugate Vaccine showed statistically significantly superior immune responsescompared to Menomune.
- At 12 months after vaccination, the percentage of responders was still statistically significantly higher after MenACWY compared with Menomune for children 2 – 10 years of age.
- Additional analyses using the responder criterion hSBA titer ≥ 1:8 showed similar results as for the hSBA titer ≥ 1:4.

2. Toddlers Aged 12 to 23 Months

- As assessed by either the percentage of subjects with hSBA ≥ 1:4 or GMTs, at 1 month after vaccination MenACWY showed statistically significantly superior immune responseswhen administered to toddlers 12 to 23 months of age compared to Menomune administered to children aged 3 to 5 years.
- Analysis of toddlers who received MenACWY alone or in combination with PnC (toddlers aged 12 to 15 months) or DTaP (toddlers aged 16 to 23 months) showed no substantial differences between the groups with regard to the responder rate and GMT. Minor differences between MenACWY alone and MenACWY in combination with PnC or DTaP against serogroups A and W showed a higher responder rate and GMT for the combined vaccination than for MenACWY alone.
- Generally, additional analyses using the responder criterion hSBA titer ≥ 1:8 showed similar results as for the hSBA titer ≥ 1:4; minor differences observed between MenACWY alone and MenACWY in combination with PnC or DTaP against serogroups A and W disappeared when using the criterion hSBA titer ≥ 1:8.

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3. Safety

- Novartis MenACWY vaccine was well tolerated by 2- to 10-year-old children during the study with an adverse event profile consistent with subjects in these age groups.
- The incidence of local reactions, especially erythema and induration, was higher in the MenACWY groups than in the corresponding Menomune groups, whereas no remarkable differences in systemic reactions between the MenACWY and Menomune groups were observed. It is a somewhat expected finding that a conjugate vaccine elicits somewhat higher incidence of local reactions than a polysaccharide vaccine. Severe reactions were rare ($\leq$ 2%) in either group.
- There were no substantial differences between MenACWY and Menomune groups in the incidence or severity of any other adverse event.
- Combined vaccination of 12- to 23-month-old toddlers with MenACWY and PnC or DTaP did not significantly alter the tolerability profile of MenACWY.

Table 2-1 Time and Events: Children 2 to 10 Years of Age

Visit Number **Study Day**	**1** **1**	**☎** **3**	**2** **29**	**3** **360**
(Range)	(0)	(2 to 4 days after visit 1)	(28 to 35 days after visit 1)	(344 to 374 days after visit 1)
Procedures				
Obtain Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History	X			
Physical Assessment[a]	X		X	X
Obtain Blood Sample[b]	X		X	X
Administer Study Vaccine[c]	X			
Dispense Diary Card	X			
Dispense Worksheet			X	
Injection-site Examination[d]	X		X	X
Assess Local and Systemic Reactions[e]	X		X	
Concomitant Medications	X[f]	X[f]	X[g]	

Note: Day 1 is defined as day of study vaccination. One month is defined as 28 days.

[a] The physical assessments at visits 1, 2 and 3 (study days 1, 29 and 360) were to be performed by the study investigator or designee.

[b] 10 mL of blood were to be collected per study visit.

[c] The study vaccine, Novartis MenACWY Conjugate Vaccine, was administered IM into the subjects left deltoid or a licensed meningococcal ACWY vaccine, Menomune, was administered SC into the subject's left upper arm. All subjects were observed in the clinic for 30 minutes after vaccination. NOTE: Routine concomitant vaccines should not be administered in the same limb as the study vaccine.

[d] Inspect the study vaccine injection site at all study visits.

[e] Local and systemic reactions following vaccination were noted by subjects' parents/legal guardians in the diary cards daily for 7 days after vaccination (study days 1 through 7). The diary cards were reviewed during the study day 3 follow-up phone interview and collected at visit 2. Note: For subjects 2 to 5 years of age, axillary temperature was measured. Systemic reactions to be collected were: change in eating habits, sleepiness, irritability, vomiting, diarrhea, arthralgia, and headache. For subjects 6 to 10 years of age, oral temperature was measured. Systemic reactions to be collected were: chills, nausea, malaise, myalgia, arthralgia, and headache.

[f] Collect data on concomitant medications (prescription and non prescription) through the first 7 days after vaccination (study days 1 through 7).

[g] Collect data on concomitant medications (prescription only) from study days 8 through visit 2.

[h] From study days 1 through 7, information regarding all AEs were recorded and collected. From study day 8 through visit 2, information regarding any SAE, any event requiring a physician visit, and any event resulting in a subject's early termination were recorded and collected. From visit 2 to visit 3, any SAE, any significant medical event, and any event resulting in a subject's early termination were recorded and collected.

Table 2-2 Time and Events: Toddlers 12 to 23 Months of Age

Visit Number **Study Day**	**1** **1**	**☎** **3**	**2** **29**	**3** **360**
(Range)	(0)	(2 to 4 days after visit 1)	(28 to 35 days after visit 1)	(344 to 374 days after visit 1)
Procedures				
Obtain Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History	X			
Physical Assessment[a]	X		X	X
Obtain Blood Sample[b]	X		X	X
Administer Study Vaccine[c]	X			
Administer Concomitant Vaccine[d]	X			
Dispense Diary Card	X			
Dispense Worksheet			X	
Injection-site Examination[e]	X		X	X
Assess Local and Systemic Reactions[f]	X		X	
Concomitant Medications	X[g]	X[g]	X[h]	
Adverse Events [I]	X	X	X	X
Collect Diary Card			X	
Collect Worksheet				X
Study Termination				X

Note: Day 1 is defined as day of study vaccination. One month is defined as 28 days.

[a] The physical assessments at visits 1, 2 and 3 (study days 1, 29 and 360) were to be performed by the study investigator or designee.

[b] 5 mL of blood were to be collected per study visit.

[c] The study vaccine, Novartis MenACWY Conjugate Vaccine, was administered IM into the subjects left deltoid. All subjects were observed in the clinic for 30 minutes after vaccination. NOTE: Toddlers randomized to receive Novartis MenACWY Conjugate Vaccine alone were not to receive any other routinely administered concomitant vaccines.

[d] For subjects randomized to receive a concomitant vaccine along with Novartis MenACWY Conjugate Vaccine, the following occurred: 1) Toddlers 12 to 15 months of age were administered IM a single dose of PnC in an age/size/weight-appropriate location, or 2) Toddlers 16 to 23 months of age were administered a single dose of DTaP in an age/size/weight-appropriate location. All subjects were observed in the clinic for 30 minutes after vaccination. NOTE: For toddlers randomized to receive concomitant PnC or DTaP (depending on age group) with Novartis MenACWY Conjugate Vaccine, other age-appropriate routine concomitant vaccines were allowed. Concomitant vaccines were not to be administered in the same limb as the study vaccine.

[e] Inspect the study vaccine injection site at all study visits.

[f] Local and systemic reactions following vaccination were noted by subjects' parents/legal guardians in the diary cards daily for 7 days after vaccination (study days 1 through 7). The diary cards were reviewed during the study day 3 follow-up phone interview and collected at visit 2. Note: Axillary temperature was measured. Systemic reactions to be collected were: change in eating habits, sleepiness, persistent crying lasting >3 hours, irritability, vomiting and diarrhea.

[g] Collect data on concomitant medications (prescription and nonprescription) through the first 7 days after vaccination (study days 1 through 7).

[h] Collect data on concomitant medications (prescription only) from study days 8 through visit 2.

[i] From study days 1 through 7, information regarding all AEs were recorded and collected. From study day 8 through visit 2, information regarding any SAE, any event requiring a physician visit, and any event resulting in a subject's early termination were recorded and collected. From visit 2 to visit 3, any SAE, any significant medical event, and any event resulting in a subject's early termination were recorded and collected.

Table 2-3 **Primary Immunogenicity Variable: Percentage of Responders in Subjects Aged 2 to 10 Years (hSBA Titers ≥ 1:4) at One Month After Vaccination**

Sero-group	Day	hSBA	Vaccine Group		Diff. MenACWY 2-10 – Menomune 2-10 95% CI (%)
			MenACWY 2-10	Menomune 2-10	
A	**1**	n (%) ≥ 1:4 95% CI (%) N	6 (2) 1 – 5 280	1 (0) 0.009 – 2 281	2 0 - 4
	29	n (%) ≥ 1:4 95% CI (%) N	228 (81) 76 – 86 280	125 (44) 39 – 51 281	37 **29 - 44**
C	**1**	n (%) ≥ 1:4 95% CI (%) N	80 (28) 23-34 281	81 (29) 23-34 283	0 -8 - 7
	29	n (%) ≥ 1:4 95% CI (%) N	232 (83) 78-87 281	181 (64) 58-70 283	19 **12 - 26**
W	**1**	n (%) ≥ 1:4 95% CI (%) N	111 (40) 34-46 279	108 (38) 33-44 282	1 -7 - 10
	29	n (%) ≥ 1:4 95% CI (%) N	263 (94) 91-97 279	202 (72) 66-77 282	23 **17 - 29**
Y	**1**	n (%) ≥ 1:4 95% CI (%) N	61 (22) 17-27 280	68 (24) 19-30 282	-2 -9 - 5
	29	n (%) ≥ 1:4 95% CI (%) N	254 (91) 87-94 280	167 (59) 53-65 282	31 **25 - 38**

Bold: 95% CI completely below or above 0%
Source: [Table 11.4.1.1-1] Table 14.2.1.1. Individual subject results: Appendix 16.2.6.1.

Table 2-4 Secondary Immunogenicity Variable: Geometric Mean hSBA Titers in Subjects Aged 2 to 10 Years at One Month After Vaccination

Sero-group	Day	hSBA	Vaccine Group		*P* Value Group
			MenACWY 2-10	Menomune 2-10	
A	**1**	GMT 95% CI N	2.06 2.02-2.1 280	2.02 1.98-2.06 281	.16
	29	GMT 95% CI N	36 30-44 280	6.31 5.21-7.64 281	**< .001**
	29 / 1	GMR 95% CI N	18 15 – 21 280	3.13 2.59 – 3.7 281	**< .001**
C	**1**	GMT 95% CI N	3.07 2.77-3.4 281	3.33 3.01-3.68 283	.26
	29	GMT 95% CI N	26 21-34 281	15 12-20 283	**.002**
	29 / 1	GMR 95% CI N	8.61 6.98 – 11 281	4.63 3.76 – 5.71 283	**< .001**
W	**1**	GMT 95% CI N	5.74 4.86-6.78 279	5.63 4.77-6.65 282	.88
	29	GMT 95% CI N	60 50-71 279	14 12-17 282	**< .001**
	29 / 1	GMR 95% CI N	10 8.74-12 279	2.48 2.09-2.94 282	**<.001**
Y	**1**	GMT 95% CI N	3.32 2.95-3.73 280	3.34 2.97-3.76 282	.92
	29	GMT 95% CI N	54 44-66 280	11 9.29-14 282	**< .001**
	29 / 1	GMR 95% CI N	16 13-20 280	3.42 2.78-4.22 282	**<.001**

Bold: *P* value < .05
Source: [Table 11.4.1.2.1-1] Table 14.2.1.7. Individual subject results: Appendix 16.2.6.1.

Table 2-5 **Percentage of Responders (hSBA Titers ≥ 1:4) and Geometric Mean Titers in Subjects Aged 2 to 5 and 6 to 10 Years Who Received MenACWY or Menomune at One Month After Vaccination**

Day	Number of Responders /GMT	Children Aged 2-5 Years			Children Aged 6-10 Years		
		Vaccine Group		Diff. (%) MenACWY – Menomune 95% CI (%) / *P* Value	Vaccine Group		Diff. (%) MenACWY – Menomune 95% CI (%) / *P* Value
		MenACWY	Menomune		MenACWY	Menomune	
Serogroup A							
1	n (%)* 95% CI(%) N	2 (2) 0 - 5 133	0 (0) 0 - 3 138	2 -1 - 5	4 (3) 1 - 7 147	1 (1) 0.018 - 4 143	2 -1 - 6
29	n (%)* 95% CI(%) N	106 (80) 72 - 86 133	59 (43) 34 - 51 138	37 **26 - 47**	122 (83) 76 - 89 147	66 (46) 38 - 55 143	37 **26 - 47**
Day 29 GMT 95% CI		28 22-37	5.8 4.49-7.5	**<.001**	45 34-60	6.84 5.17-9.06	**<.001**
Serogroup C							
1	n (%)* 95% CI(%) N	31 (23) 16 - 31 135	15 (11) 6 - 17 138	12 **3 – 21**	49 (34) 26 - 42 146	66 (46) 37 - 54 145	-12 **-23 – -1**
29	n (%)* 95% CI(%) N	103 (76) 68 - 83 135	62 (45) 36 - 54 138	31 **20 – 42**	129 (88) 82 - 93 146	119 (82) 75 - 88 145	6 -2 – 15
Day 29 GMT 95% CI		14 11-19	6.93 5.22-9.18	**<.001**	47 34-67	33 23-47	**.15**
Serogroup W							
1	n (%)* 95% CI(%) N	43 (32) 24 - 40 135	31 (22) 16 – 30 138	9 -1 - 20	68 (47) 39 - 56 144	77(53) 45 - 62 144	-6 -18 - 5
29	n (%)* 95% CI(%) N	122 (90) 84 - 95 135	76 (55) 46 - 64 138	35 **26 - 45**	141 (98) 94 - 100 144	126 (88) 81 - 92 144	10 **5 - 17**
Day 29 GMT 95% CI		43 34-56	7.84 6.12-10	**<.001**	80 65-99	24 20-30	**< .001**
Serogroup Y							
1	n (%)* 95% CI(%) N	24 (18) 12 - 25 134	18 (13) 8 - 20 138	5 -4 – 14	37 (25) 19 - 33 146	50 (35) 27 - 43 144	-9 -20 - 1
29	n (%)* 95% CI(%) N	116 (87) 80 - 92 134	67 (49) 40 - 57 138	38 **28 – 48**	138 (95) 89 - 98 146	100 (69) 61 - 77 144	25 **17 - 34**
Day 29 GMT 95% CI		42 31-56	7.17 5.37-9.58	**< .001**	68 51-90	18 13-24	**< .001**

* n (%) hSBA ≥ 1:4
Bold: 95% CI completely below or above 0% or *P* value < .05
Source: [Table 11.4.1.2.2-1] Tables 14.2.1.2, 14.2.1.3, 14.2.1.8, 14.2.1.9

Table 2-6 Percentage of Responders (hSBA Titers ≥ 1:4) and Geometric Mean hSBA Titers in Toddlers Aged 12 to 23 Months Who Received MenACWY Compared to Children Aged 3 to 5 Years Who Received Menomune at One Month After Vaccination

Sero-group	Day	hSBA	Vaccine Group		Diff. Men ACWY – Meno-mune (%) 95% CI (%)	hSBA	Vaccine Group		*P* Value Group
			Men ACWY 12-23	Meno-mune 3-5			Men ACWY 12-23	Meno-mune 3-5	
A	**1**	n (%) ≥ 1:4 95% CI (%) N	0 (0) 0-2 240	0 (0) 0-4 91	0 -4-2	Day 29 GMT 95% CI N	18 15-21	7.18 5.34-9.64	**<.001**
	29	n (%) ≥ 1:4 95% CI (%) N	195 (81) 76-86 240	46 (51) 40-61 91	31 **19-42**				
C	**1**	n (%) ≥ 1:4 95% CI (%) N	8 (3) 1-6 241	11 (12) 6-21 91	-9 **-17- -3**	Day 29 GMT 95% CI N	22 18-26	7.09 5.29-9.5	**<.001**
	29	n (%) ≥ 1:4 95% CI (%) N	218 (90) 86-94 241	38 (42) 32-53 91	49 **38-59**				
W	**1**	n (%) ≥ 1:4 95% CI (%) N	7 (3) 1-6 240	22 (24) 16-34 91	-21 **-31- -13**	Day 29 GMT 95% CI N	18 15-21	9.52 7.21-13	**<.001**
	29	n (%) ≥ 1:4 95% CI (%) N	207 (86) 81-90 240	57 (63) 52-73 91	24 **13-35**				
Y	**1**	n (%) ≥ 1:4 95% CI (%) N	5 (2) 1-5 238	14 (15) 9-24 91	-13 **-22- -7**	Day 29 GMT 95% CI N	11 8.91-14	8.48 6.01-12	**.20**
	29	n (%) ≥ 1:4 95% CI (%) N	153 (64) 58-70 238	46 (51) 40-61 91	14 **2-25**				

Bold: 95% CI completely below or above 0% or *P* value < .05
Source: [Table 11.4.1.2.3-1] Table 14.2.1.10 and Table 14.2.1.24

Table 2-7 **Percentage of Responders (hSBA Titers ≥ 1:4) and Geometric Mean hSBA Titers in Subjects Aged 2 to 10 Years at 12 Months After Vaccination**

Sero-group	Day	hSBA	Vaccine Group		Diff. (%) MenACWY – Menomune 95% CI (%)	hSBA	Vaccine Group		*P* Value Group
			Men ACWY 2-10	Meno-mune 2-10			Men ACWY 2-10	Meno-mune 2-10	
A	**360**	n (%) ≥ 1:4 95% CI (%) N	71 (28) 23 – 34 253	44 (18) 14 – 24 238	10 **2 - 17**	Day 360 GMT 95% CI N	3.88 3.394.44 253	3 2.61-3.44 238	**.009**
C	**360**	n (%) ≥ 1:4 95% CI (%) N	172 (68) 62 - 74 252	126 (53) 46 - 59 240	16 **7 - 24**	Day 360 GMT 95% CI N	11 8.64-13 252	9.02 7.23-11 240	**.27**
W	**360**	n (%) ≥ 1:4 95% CI (%) N	234 (94) 90 - 97 249	119 (50) 44 - 57 237	44 **37 – 51**	Day 360 GMT 95% CI N	42 35-50 249	7.57 6.33-9.07 237	**< .001**
Y	**360**	n (%) ≥ 1:4 95% CI (%) N	215 (86) 81 - 90 250	90 (38) 31 - 44 239	48 **41 – 56**	Day 360 GMT 95% CI N	27 22-33 250	5.29 4.34-6.45 239	**< .001**

Bold: 95% CI completely below or above 0% or *P* value < .05
GMR: GMT 12 months post vaccination/ GMT pre-vaccination
Source: [Table 11.4.1.2.4-1] Tables 14.2.1.31 and 14.2.1.37

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines & Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate VaccineMenA	VOLUME: PAGE:	
Name of Active Ingredient CRM_{197}-MenA conjugate, CRM_{197}-MenC conjugate, CRM_{197}-MenW-135 conjugate, CRM_{197}-MenY conjugate	Study number: V59P9	

Title of Study: A Phase 2, Partially Randomized, Open Label, Multicenter Study to Evaluate the Safety and Immunogenicity after One or Two Doses of Chiron Meningococcal ACWY Conjugate Vaccine Administered to Healthy Infants and Young Children

Protocol Number: V59P9

Investigators: Dr. Scott Halperin and Dr. Francisco Diaz-Mitoma

Study Centers: Clinical Trials Research Center, Department of Pediatrics, Dalhousie University, Halifax, B3K 6R8, Canada; Herridge Community Health Clinic, Ottawa, Ontario, K1S 0G8, Canada; Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, K1H 8L1, Canada

Publication (reference): Safety and Immunogenicity of Novartis Vaccines MenACWY Conjugate Vaccine after One or Two Doses Administered to Infants and Young Children. WSPID abstract, May 30 2007. SA Halperin, F Diaz-Mitoma, A Anemona, F Ceddia.

Study Period: (date of first enrollment) 22 JUN 05 (date of last completed) 29 NOV 06	**Phase of Development:** Phase 2

Objectives:

Primary Immunogenicity Objective:

To assess the immunogenicity of Novartis MenACWY conjugate vaccine (MenACWY) when administered as a two-dose schedule at 6 and 12 months of age, where immunogenicity was defined as a serum bactericidal assay titer using human complement (hSBA) of 1:4 or greater (i.e., the percentage response) against *N meningitidis* serogroups A, C, W, and Y at one month after the second vaccination.

Secondary Immunogenicity Objectives:

- To assess the immunogenicity of MenACWY vaccine when administered as a two-dose schedule at 6 and 12 months of age, where immunogenicity was defined by: (a) hSBA geometric mean titer (GMT); and (b) percent response 1:8 or greater against *N meningitidis* serogroups A, C, W, and Y.
- To assess the immunogenicity of MenACWY vaccine when administered as a one-dose

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schedule at 12 months of age, where immunogenicity was defined by: (a) hSBA GMT; and (b) percent response of 1:8 or greater against *N meningitidis* serogroups A, C, W, and Y.

- To assess the immunogenicity response of the DTaP-Hib-IPV and PC7 routine vaccinations when administered alone or concomitantly with MenACWY vaccine at 6 months of age.
- To evaluate the immune response of MenC conjugate vaccine administered at 12 months of age, where immune response was defined by: (a) percent response of 1:4 or greater; (b) percent response of 1:8 or greater; and (c) hSBA GMT against *N meningitidis* serogroup C.
- To evaluate the primary immunogenicity of the A, W, Y component of MenACWY vaccine when administered at 18 months of age following one dose of MenC conjugate vaccine previously administered at 12 months of age, where immunogenicity was defined by: (a) percent response of 1:4 or greater; (b) percent response of 1:8 or greater; and (c) hSBA GMT against *N meningitidis* serogroups A, W, and Y.
- To evaluate the booster response of the C component of MenACWY vaccine when administered at 18 months of age following one dose of MenC conjugate vaccine previously administered at 12 months of age, where immunogenicity was defined by: (a) percent response of 1:4 or greater; (b) percent response of 1:8 or greater; and (c) hSBA GMT against *N meningitidis* serogroup C.

Safety Objective:

To evaluate the safety and tolerability of the study and concomitant vaccines in all study subjects.

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Name of Active Ingredient CRM_{197}-MenA conjugate, CRM_{197}-MenC conjugate, CRM_{197}-MenW-135 conjugate, CRM_{197}-MenY conjugate	Study number: V59P9	

Methodology:

This was a phase 2, open-label, active-controlled, multicenter, partially randomized study in healthy infants and toddlers. Subjects were included in the study if in good health as judged by physical examination and medical history, and if they met all inclusion criteria and no exclusion criteria.

Approximately 200 subjects up to 6 months old at time of enrollment were randomized in a 1:1 ratio to one of two vaccination groups (group I [ACWY 6-12m] or II [ACWY 12m]). Subjects in group ACWY 6-12m received one dose of MenACWY vaccine at 6 months of age and one dose at 12 months of age. The MenACWY was given concomitantly with routine infant immunizations DTaP-Hib-IPV (Pentacel™) and 7-valent pneumococcal conjugate vaccine (PC7, Prevnar™) at 6 months of age and with PC7 at 12 months of age. Subjects in group ACWY 12m did not receive MenACWY at 6 months of age (only DTaP-Hib-IPV and PC7), but did receive one dose of MenACWY vaccine at 12 months of age concomitantly with PC7. Approximately 50 subjects up to 12 months old at the time of enrollment were included in group III (C12 ACWY18) and received one dose of the Novartis MenC conjugate vaccine (Menjugate™) concomitantly with PC7. A single dose of MenACWY vaccine was then administered to all subjects belonging to group C12 ACWY18 at 18 months of age concomitantly with DTaP-Hib-IPV. Measles, mumps, rubella (MMR), and varicella routine vaccines were to be administered to all subjects at 13 months of age, after the blood draw, but were not a part of the study assessments. The study MenACWY and control Menjugate vaccines were administered intramuscularly (IM) into the anterolateral area of the right thigh (groups ACWY 6-12m and ACWY 12m) or into the anterolateral area of the right arm (group C12 ACWY18). Study and control vaccines were administered concomitantly with routine vaccines. Routine pediatric vaccines were administered either IM or subcutaneously (SC) (following the summary of product characteristics and local recommendations) into the anterolateral area of the left thigh or in the left arm according to Canadian procedures. Study groups and vaccines are summarized in the following table.

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Visit		**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Months of age		**6**	**7**	**12**	**13**
Group	**I** ACWY 6-12m	Serology **MenACWY** PC7 DTaP-Hib-IPV	Serology	Serology **MenACWY** PC7	Serology MMR+Varicella[a]
	II ACWY 12m	Serology PC7 DTaP-Hib-IPV	Serology	Serology **MenACWY** PC7	Serology MMR+Varicella[a]
Months of age		**12**	**13**	**18**	**19**
	III C12 ACWY18	Serology **MenC** PC7	Serology MMR+ Varicella[a]	Serology **MenACWY** DTaP-Hib-IPV	Serology

[a] Measles, mumps, rubella and/or Varicella vaccines were administered after blood draw and were not a part of the study assessment.

All subjects were observed for 30 minutes following each immunization to assess immediate hypersensitivity reactions. The parents/legal guardians of the subjects were instructed to complete a diary card for both local reactions (tenderness, erythema, and induration) and systemic reactions (change in eating habits, sleepiness, vomiting, diarrhea, and irritability) for 7 days following each vaccination. During this period, axillary temperature was also to be recorded on a daily basis (at the same time each day, whenever possible). A telephone call was made to check the subject's status 2 days (day 3, window +2) and 7 days (day 8, window +4) after each vaccination. The diary cards were collected, and the data were reconciled during the next site visit.

Blood samples (3 to 5 mL) for evaluating serum antibody responses to *N meningitidis* serogroups A, C, W, and Y, as measured by hSBA, were to be drawn from all subjects before and 28 days after each vaccination.

All adverse events (AEs) were to be collected for 7 days following each vaccination. From visit

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1 to visit 2 and from visit 3 to visit 4, study personnel collected and recorded the following events: serious adverse events (SAEs), AEs necessitating a physician's visit or leading to Emergency Room visit, and AEs resulting in premature withdrawal of subjects from the study. From visit 2 to visit 3, a monthly telephone call was made to check the subject's health, and a follow-up phone call to assess the subject's health status was performed 6 months after the last study vaccination. During these phone calls, SAEs were recorded; however, the following were not recorded: preplanned visits; medical office visits for routine medical care and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries). During the study, all reported AEs were to be followed until resolution or diagnosis. If an AE remained unresolved at the conclusion of the study, the investigator and medical monitor made a clinical assessment about whether continued follow-up of the AE was warranted.

All vaccinations received since birth, and all prescription medications given during the 6 months before enrollment, were recorded. All prescription and nonprescription medications (with the exception of minerals, homeopathic medications, supplements, and vitamins) taken by the subjects during the first 7 days following each vaccination were to be recorded. From visit 1 to visit 2 and from visit 3 to visit 4, any prescription and nonprescription medications (with the exception of minerals, homeopathic medications, supplements, and vitamins) taken for treatment of any SAE and AE were to be recorded. From visit 2 to visit 3, any prescription and nonprescription medications (with the exception of minerals, supplements, and vitamins) for the treatment of SAEs were to be reported. During the 6-month follow-up period, prescription and nonprescription medications (with the exception of minerals, supplements, and vitamins) taken by the subject for treatment of SAEs, and medically significant AEs requiring a physician's visit or leading to an Emergency Room visit, were to be recorded.

Number of Subjects (planned and analyzed): A total of 250 healthy subjects were planned for enrollment in this study. A total of 175 subjects were enrolled and analyzed in this study.

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria (Groups I and II)

Subjects eligible for enrollment in groups I and II of the study were healthy infants 6 months old:

1. who were born after full term pregnancy with an estimated gestational age of 37 weeks or greater and a birth weight 2.5 kg or greater;
2. who previously received two doses of PC7 and DTaP-Hib-IPV vaccines;
3. for whom a parent/legal guardian gave written informed consent, after the nature of the study was explained;
4. who were available for all the visits scheduled in the study;
5. who were in good health as determined by medical history, physical examination, and clinical judgment of the investigator.

Inclusion Criteria (Group III)

Subjects eligible for enrollment in the study were healthy subjects 12 months old:

1. who were 12 months old;
2. who previously received three doses of DTaP-Hib-IPV vaccines;
3. for whom a parent/legal guardian gave written informed consent, after the nature of the study was explained;
4. who were available for all the visits scheduled in the study;
5. who were in good health as determined by medical history, physical examination, and clinical judgment of the investigator.

Exclusion Criteria (All groups)

Individuals were not to be included in this study if:

1. their parents/legal guardians were unwilling or unable to give written informed consent to participate in the study;
2. they previously received any meningococcal vaccine;
3. they had a previously ascertained or suspected disease caused by *N meningitidis*;
4. they had a history of any anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations, or known hypersensitivity to any vaccine component;

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5. they had experienced significant acute or chronic infection within the previous 7 days or had experienced fever (38.0ºC or greater) within the previous 3 days;
6. they had any present or suspected serious acute disease (e.g., leukemia, lymphomas), or chronic disease (e.g., with signs of cardiac failure, renal failure, severe malnutrition, or insulin-dependent diabetes), or progressive neurological disease, or a genetic anomaly or known cytogenic disorder (e.g., Down's syndrome), or who had a diagnosed cardiac defect or abnormality of hemodynamic significance (e.g., ventricular septal defect, patent ductus arteriosus, or atrial septal defect);
7. they had a known or suspected autoimmune disease or impairment /alteration of immune function resulting from (for example):
   - any immunosuppressive therapy since birth;
   - immunostimulants since birth;
   - any systemic corticosteroid administered for more than 5 days or in a daily dose of greater than 1 mg/kg/day prednisone or equivalent for 5 days or less in the previous 30 days;
8. they had a suspected or known HIV infection or HIV-related disease;
9. they had received parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the past 90 days and were expected to receive it for the full length of the study;
10. they had a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
11. they had a history of seizure disorder:
12. a. febrile seizure;
13. b. any other seizure disorder;
14. they had taken systemic antibiotics (either oral or parenteral) within the previous 14 days (EXCEPTION: subjects who had received an oral or parenteral β-lactam antibiotic [e.g., penicillin, amoxicillin, ceftriaxone, cefuroxime, or cephalexin] could have been enrolled 7 days following the last dose);
15. their parents/legal guardians were planning to leave the area of the study site before the end of the study period;
16. they had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

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Test Product, Dose, Mode of Administration, Lot Number:

The investigational Novartis MenACWY vaccine was obtained by extemporaneous mixing just before injection of the lyophilized MenA (Lot number 002011) with the MenCWY full liquid vaccine (Lot number U79P33D1).

MenACWY vaccines were administered by IM injection into the anterolateral area of the right thigh (**group ACWY 6-12m** and **group ACWY 12m**) or into the anterolateral area of the right arm (**group C12 ACWY18**).

After reconstitution, MenACWY vaccine had the following composition per 0.5 mL of injectable solution:

Name of Ingredients	**Quantity per Dose**
CRM_{197}-MenA conjugate	10 µg MenA (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW (b) (4) CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY (b) (4) CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
(b) (4)	

CRM = cross-reactive material

Duration of Study: The total duration of this study was approximately 13.5 months. Subjects were enrolled over an 8–week period, and each subject participated for 12 months.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Group C12 ACWY18 subjects received Novartis Menjugate. Menjugate vaccine was obtained by extemporaneous mixing just before injection of the lyophilized MenC component (Lot number UA9477AF) and a saline solvent (Lot number 045131). After reconstitution, Menjugate had the following composition per 0.5 mL of injectable solution.

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Name of Ingredients	**Quantity per Dose**
CRM197-MenC conjugate	10 µg MenC 12.5-25 µg CRM_{197}
Aluminum hydroxide	1.0 mg
Sodium chloride	3.5 mg
Mannitol	7.3 mg
Sodium phosphate monobasic	0.92 mg
Sodium phosphate dibasic	0.48 mg

Dosage: 0.5 mL dose of Menjugate was administered by IM injection in the arm region.

Concomitant Vaccines

Diphtheria, Tetanus, acellular Pertussis, *H Influenzae* type b, Inactivated Polio, DTaP-IPV-Hib, MMR, Varicella, and PC7 were those regularly administered according to recommended vaccination schedule for infants and toddlers.

Criteria for Evaluation:

Immunogenicity

The ability of MenACWY conjugate vaccine to elicit functional bactericidal antibody titers against each serogroup as measured by hSBA was evaluated. The immunogenicity measures were the anti-*N meningitidis* serogroup A, C, W, and Y percentage of who had hSBA of 1:4 or greater (primary), hSBA of 1:8 or greater (secondary), and hSBA GMT.

Safety

Measures of safety and reactogenicity included data from observed local reactions (tenderness, erythema, and induration) and systemic reactions (change in eating habits, sleepiness, vomiting, diarrhea, and irritability). These data were collected together with axillary temperature, analgesic/antipyretic medication use, and all AEs during the first 7 days after each test vaccine or reference vaccine injection. After 7 days and until next study visit, adverse events necessitating a physician's visit or leading to Emergency Room visit and/or resulting in premature withdrawal of subject from the study were to be collected and recorded by study personnel during each of the study visits (applicable from visit 1 to visit 2, and from visit 3 to visit 4). Serious adverse events and medically significant AE requiring a physician visit or leading to Emergency Room visit were to be collected throughout the study (preplanned visits,

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medical office visits for routine medical care, and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries were not to be collected from visit 2 to visit 3 and after visit 4).

Statistical Methods:

Immunogenicity

There was no statistical null hypothesis associated with the primary immunogenicity objective. All immunogenicity analyses were run descriptively. The primary measure of immunogenicity for each serogroup was the percentage of subjects with hSBA titers of 1:4 or greater at one month after the second vaccination. The secondary measures of immunogenicity for each serogroup were the percentage of subjects with hSBA titer of 1:4 or greater, 1:8 or greater, and hSBA GMTs at baseline and at one month after the vaccination.

Safety

Safety was assessed in terms of the number of subjects with reported local and systemic reactions as well as the number of subjects with reported SAEs and/or all AEs up to 7 days after each vaccination and/or AEs requiring a physician's visit and/or resulting in premature withdrawal from the study, per vaccination group. After 7 days and until next study visit, adverse events necessitating a physician's visit or leading to Emergency Room visit and/or resulting in premature withdrawal of subject from the study were collected and recorded by study personnel during each of the study visits (applicable from visit 1 to visit 2, and from visit 3 to visit 4). Serious adverse events and medically significant AE requiring a physician visit or leading to Emergency Room visit were collected throughout the study (preplanned visits, medical office visits for routine medical care and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries were not collected from visit 2 to visit 3 and after visit 4). All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 7.1, and grouped by MedDRA preferred terms into frequency tables according to MedDRA system-organ-class categories and preferred term classifications.

Interim Analysis

To facilitate the planning of future trials, when all subjects had completed visit 2, a group-unblinded interim analysis was to be performed for the evaluation of immunogenicity. In addition, a preliminary analysis was to be performed to assess immunogenicity and 1-month safety (including local and systemic postimmunization reactions within 7 days of

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immunization), after all subjects had completed visit 4. The results of these analyses were not to alter the course of the trial. The analyses were governed by the procedures specified in the Novartis document entitled "Interim Analysis in a Clinical Trial."

Summary and Conclusions:
Immunogenicity results:

Primary analyses of the two-dose MenACWY group ACWY 6-12m (group I): In the ACWY 6- to 12-month vaccine group (group I), the persistence of hSBA titers after the first vaccination of MenACWY (visit 1) was still apparent before the second vaccination at 12 months of age (visit 3) against C, W, and Y (85%, 85%, and 72%), but not A (10%), serogroups (Table 2.0-2). In the primary analysis, after the second MenACWY vaccination at 12 months of age in the ACWY 6-12m group, the percentages of subjects with hSBA titers of 1:4 or greater showed that two vaccinations with MenACWY at 6 and 12 months of age were highly immunogenic (88%, 100%, 100%, and 100% against A, C, W, and Y serogroups, respectively).

Secondary analyses of the two-dose MenACWY group ACWY 6-12m (group I): Confirming the primary analysis, GMTs for the ACWY 6- to 12-month group were significantly elevated after two vaccinations of MenACWY 6 months apart against all four serogroups (Table 2.0-3: GMT = 44, 302, 220, and 136 against A, C, W, and Y serogroups, respectively). GMRs ranged from 15- to 18-fold increases in GMTs against the four serogroups at 12 months of age compared to those at 6 months of age. Percentages of subjects with hSBA titers of 1:8 or greater (Table 2.0-4: percentage with hSBA of 1:8 or greater: 84%, 100%, 100%, and 100% against A, C, W, and Y serogroups, respectively) further supported the conclusion that two vaccinations of MenACWY 6 months apart produced highly immunogenic results against all four serogroups and that the 1:8 results were very similar to results obtained using the 1:4 threshold.

Secondary analyses of the one-dose MenACWY group ACWY 12m: GMTs after one vaccination of MenACWY at 12 months increased against all four serogroups (11, 40, 30, and 10 against A, C, W, and Y, respectively) but were lower than the ACWY 6-12m two-vaccination group (44, 302, 220, and 136), indicating that the ACWY 6-12m two-vaccination group was more highly immunogenic than the one-vaccination ACWY 12m group. GMRs in the ACWY 12-month vaccine group ranged from 5.17- to 20-fold increases against the four serogroups. Percentages of subjects with hSBA titers of 1:8 or greater (60%, 93%, 93%, and 67% against A, C, W, and Y serogroups, respectively) were very similar to results obtained for the 1:4 threshold and less than the ACWY 6-12 two-dose group for all serogroups.

Name of Sponsor Novartis Vaccines & Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate VaccineMenA	VOLUME: PAGE:	
Name of Active Ingredient CRM_{197}-MenA conjugate, CRM_{197}-MenC conjugate, CRM_{197}-MenW-135 conjugate, CRM_{197}-MenY conjugate	Study number: V59P9	

Secondary analyses of MenC against the C serogroup: MenC with concomitant Prevnar at 12 months of age (C12 ACWY18 group) induced significant increases in GMTs against serogroup C at 13 months of age. The mean GMT at 13 months of age was 19-fold above the mean GMT before vaccination at 12 months of age (visit 1). Percentages of subjects with hSBA of 1:4 and 1:8 or greater showed that MenC with concomitant Prevnar at 12 months of age was highly immunogenic 1 month later (93% and 88%, respectively).

Secondary analyses of MenACWY after MenC against A, W, and Y serogroups: As expected, there were neglible hSBA titers against serogroups A, W, and Y prior to vaccination with MenACWY at 18 months of age (group C12 ACWY18). One month after vaccinations at 19 months of age, GMTs (8.05, 17, and 13) and percentages of subjects with hSBA of 1:4 or greater (63%, 81%, and 79%) and of 1:8 or greater (50%, 76%, and 63%) showed significant immunogenicity against A, W, and Y serogroups, respectively.

Secondary analyses of the booster response of the C component of MenACWY: Group C12 ACWY18 subjects who received a single injection of MenC with concomitant Prevnar at 12 months of age exhibited significant increases in GMT against serogroup C at 13 months of age (visit 2 GMT = 39, GMR = 19) and percentages of subjects with hSBA of 1:4 or greater (93%) and 1:8 or greater (88%). Group C12 ACWY18 results obtained at visit 3 and visit 4 showed that a MenACWY booster effect against serogroup C at 19 months of age was highly immunogenic and was greater than the original persistence effect at 13 months of age. Before a single vaccination of MenACWY at 18 months of age, the C12 ACWY18 vaccine group showed persistence of hSBA titers against serogroup C (visit 3 GMT = 29) and in the percentage of subjects who achieved the 1:4 or greater threshold (89%) and the 1:8 or greater threshold (82%). One month later at 19 months of age (1 month after MenACWY vaccination), GMT was 667, GMR was 23, percentage of subjects with hSBA of 1:4 or greater was 100%, and percentage of subjects with hSBA of 1:8 or greater was 100%.

Safety results:

The incidence of any reaction, any local reaction, and any systemic reaction was similar among the three vaccine groups (any reaction: 97%, 95%, and 100% of subjects in ACWY 6-12m, ACWY 12m, and C12 ACWY18 vaccine groups, respectively; local reactions: 83%, 80%, and 94%; systemic reactions: 92%, 90%, and 86%). Local and systemic reactions were transient and mild to moderate in intensity.

Previous vaccinations of routine vaccines with or without MenACWY at 6 months of age had no significant effect on the incidence of local tenderness, erythema, or induration after the 12-month vaccination or on the incidence of any or individual systemic reactions observed after the MenACWY 6-month or 12-month vaccination. The incidence of local and systemic reactions in

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Name of Active Ingredient CRM_{197}-MenA conjugate, CRM_{197}-MenC conjugate, CRM_{197}-MenW-135 conjugate, CRM_{197}-MenY conjugate	Study number: V59P9	

the ACWY 6-12m and ACWY 12m groups was also similar to that observed after the 12-month vaccination with the licensed MenC (Menjugate) vaccine (group C12 ACWY18). The incidence of severe local reactions following MenACWY vaccinations was low and similar to incidence following the MenC control.

There were no deaths reported during the study period from first subject first visit (June 22, 2005) to last subject last visit (November 2006).

Seven subjects experienced nine SAEs during the study, including three subjects in group ACWY 6-12m and two subjects each in groups ACWY 12m and C12 ACWY18. None of the SAEs was considered related to a study vaccine by the investigator.

None of the subjects was withdrawn from the study due to AEs, and none of the subjects experienced interruption or delay in vaccination due to AEs.

At least one AE was experienced by 48% of subjects in group ACWY 6-12m, by 48% of subjects in group ACWY 12m, and by 50% of subjects in group C12 ACWY18. No significant differences in the incidence of AEs was observed among the three study groups. AEs reported by the greatest number and percentage of subjects per vaccine group were nasopharyngitis (9%, 8%, and 8% in groups ACWY 6-12m, ACWY 12m, and C12 ACWY18, respectively). Additional AEs experienced by three or more subjects in a group included pyrexia (2% to 8%); irritability and vomiting (each 2% to 6%); constipation, upper respiratory tract infection, and eating disorder (each 2% to 5%); and cough (0% to 5%).

Three of 175 subjects experienced severe AEs during the study; none of these events was considered related to study vaccines.

Adverse events that were considered to be possibly or probably related to the study vaccine were experienced by four subjects (6%) in group ACWY 6-12m, five subjects (8%) in group ACWY 12m, and five subjects (10%) in group C12 ACWY18. Injection site erythema, injection site rash, irritability, pyrexia, poor quality sleep, eating disorder, and rash were the only vaccine related AEs reported for more than one subject. No related AEs were experienced by more than three subjects.

Conclusions:

MenACWY was well tolerated and immunogenic using different dosing regimens in infants and young children, including administration after prior vaccination with MenC. Comparable immunogenicity for serogroup C was demonstrated after a single dose of MenACWY and a single dose of Menjugate at 12 months of age.

Table 2.0-1 Time and Events

Visit Number Study Day	S -30/1	V1 1	☎ (1) 3	☎ (2) 8	V2 28	☎ (3) 56	☎ (4) 84	☎ (5) 112	☎ (6) 140	V3 168	☎ (7) 170	☎ (8) 175	V4 196	☎ (9) 336
(Range)	From 30 days before V1		2-4 days after V1	7-11 days after V1	28-42 days after V1	28-42 days after V2	28-42 days after ☎ 3	28-42 days after ☎ 4	28-42 days after ☎ 5	28-42 days after ☎ 6	2-4 days after V3	7-11 days after V3	28-42 days after V3	180 ± 14 days after V3
Procedures														
Informed consent	X	X												
Medical history		X												
Physical examination/ health assessment[a]		X								X				
Inclusion/exclusion criteria[a]		X								X				
Blood sample		X			X[b]					X			X[b]	
Vaccination		X								X				
Injection-site examination		X								X				
Local and systemic reactions		X	X	X						X	X	X		
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Data reconciliation[c]					X					X			X	
Study termination[d]													X[d]	

Note: Day 1 was defined as day of first study vaccination. Subjects in group ACWY 6-12m and II received their first vaccination at 6 months of age. Subjects in group C12 ACWY18 received their first vaccination at 12 months of age.

[a] = performed by a study investigator at visit 1 and by study investigator or delegated study nurse at visit 3.

[b] = MMR and Varicella vaccines were administered after blood draw at visit 2 for group C12 ACWY18 and at visit 4 for groups I and II, but were not part of the study assessment.

[c] = information obtained by diary cards and telephone follow-up was reconciled in the related CRF page.

[d] = early termination was allowed at any time during the study. The reasons for ending study participation were recorded in source documents and CRF.

Table 2.0-2 **Primary Immunogenicity Variable: MenACWY Two-Dose Schedule at Six and Twelve Months of Age (Group I): Percentage of Subjects With hSBA Titers of 1:4 or Greater Against N meningitidis Serogroups A, C, W, and Y at Visit 3 and Visit 4**

Serogroup	Visit	Parameter	Vaccine Group		
			Group I ACWY 6-12m	**Group II[a] ACWY 12m**	**Group III C12 ACWY18**
A	**Visit 3 12 or 18 mo of age**	n (%) ≥ 1:4 95% CI (%) N	5 (10) 3-22 50	0 0-7 53	0 0-9 38
	Visit 4 13 or 19 mo of age	n (%) ≥ 1:4 95% CI (%) N	**44 (88)** 76-95 50	**39 (74)** 60-85 53	**24 (63)** 46-78 38
C	**Visit 3 12 or 18 mo of age**	n (%) ≥ 1:4 95% CI (%) N	47 (85) 73-94 55	1 (2) 0.047-10 54	34 (89) 75-97 38
	Visit 4 13 or 19 mo of age	n (%) ≥ 1:4 95% CI (%) N	**55 (100)** 94-100 55	**52 (96)** 87-100 54	**38 (100)** 91-100 38
W	**Visit 3 12 or 18 mo of age**	n (%) ≥ 1:4 95% CI (%) N	34 (85) 70-94 40	1 (2) 0.062-13 41	1 (3) 0.068-14 37
	Visit 4 13 or 19 mo of age	n (%) ≥ 1:4 95% CI (%) N	**40 (100)** 91-100 40	**39 (95)** 83-99 41	**30 (81)** 65-92 37
Y	**Visit 3 12 or 18 mo of age**	n (%) ≥ 1:4 95% CI (%) N	38 (72) 58-83 53	0 0-7 54	0 0-9 38
	Visit 4 13 or 19 mo of age	n (%) ≥ 1:4 95% CI (%) N	**53 (100)** 93-100 53	**42 (78)** 64-88 54	**30 (79)** 63-90 38

Source: Table 14.2.1.1.3. Individual subject results: Appendix 16.2.6.1.
Note: Visit 4 was performed 1 month after the second vaccination (at visit 3).
CI = confidence interval; n = number of responders; N = number of patients with data at visits 3 and 4 per vaccine group (percentages were based on n/N).
[a] Group II vaccination 1: DtaP-Hib-IPV at 6 months

Table 2.0-3 Geometric Mean hSBA Titers in MenACWY Two-Dose Subjects at Visit 3 and Visit 4, Including Visit 4 Geometric Mean Ratio

Sero group	Visit	Parameter	Vaccine Group		
			Group I ACWY 6-12m	Group II[a] ACWY 12m	Group III C12 ACWY18
A	Visit 3 12 or 18 mo of age	GMT	2.41	1.99	2
		95% CI	2.18-2.65	1.81-2.19	1.78-2.24
		N	50	53	38
	Visit 4 13 or 19 mo of age	GMT	44	11	8.05
		95% CI	29-65	7.55-16	5.11-13
		N	50	53	38
	Visit 4/ Visit 3	GMR	18	5.56	4.03
		95% CI	12-27	3.83-8.08	2.6-6.27
		N	50	53	38
C	Visit 3 12 or 18 mo of age	GMT	19	2.06	29
		95% CI	14-25	1.54-2.77	20-41
		N	55	54	38
	Visit 4 13 or 19 mo of age	GMT	302	40	667
		95% CI	224-405	30-54	467-952
		N	55	54	38
	Visit 4/ Visit 3	GMR	16	20	23
		95% CI	12-21	15-26	17-32
		N	55	54	38
W	Visit 3 12 or 18 mo of age	GMT	15	2.09	2.09
		95% CI	12-19	1.68-2.6	1.66-2.64
		N	40	41	37
	Visit 4 13 or 19 mo of age	GMT	220	30	17
		95% CI	155-313	21-43	12-24
		N	40	41	37
	Visit 4/ Visit 3	GMR	15	14	8.08
		95% CI	10-22	9.91-21	5.42-12
		N	40	41	37
Y	Visit 3 12 or 18 mo of age	GMT	7.91	2.02	2
		95% CI	6.64-9.43	1.7-2.4	1.62-2.45
		N	53	54	38
	Visit 4 13 or 19 mo of age	GMT	136	10	13
		95% CI	100-185	7.68-14	8.78-18
		N	53	54	38
	Visit 4/ Visit 3	GMR	17	5.17	6.34
		95% CI	13-23	3.84-6.96	4.45-9.03
		N	53	54	38

Source: Table 14.2.1.3.3. Individual subject results: Appendix 16.2.6.1.
Note: Visit 4 was performed 1 month after second vaccination (at visit 3).
GMT = geometric mean titer; GMR = geometric mean ratio; CI = confidence interval; n = number of responders; N = number of patients with data at visits 3 and 4 per vaccine group (percentages were based on n/N).
[a] Group II vaccination 1: DtaP-Hib-IPV at 6 months

Table 2.0-4 Percentages of MenACWY Two-Dose Subjects With hSBA Titers of 1:8 or Greater Against *N meningitidis* Serogroups A, C, W, and Y at Visit 3 and Visit 4

Serogroup	Visit	hSBA	Vaccine Group		
			Group I ACWY 6-12m	**Group II[a] ACWY 12m**	**Group III C12 ACWY18**
A	**Visit 3**	n (%) ≥ 1:8 95% CI (%) N	4 (8) 2-19 50	0 0-7 53	0 0-9 38
	Visit 4	n (%) ≥ 1:8 95% CI (%) N	**42 (84)** 71-93 50	**32 (60)** 46-74 53	**19 (50)** 33-67 38
C	**Visit 3**	n (%) ≥ 1:8 95% CI (%) N	41 (75) 61-85 55	1 (2) 0.047-10 54	31 (82) 66-92 38
	Visit 4	n (%) ≥ 1:8 95% CI (%) N	**55 (100)** 94-100 55	**50 (93)** 82-98 54	**38 (100)** 91-100 38
W	**Visit 3**	n (%) ≥ 1:8 95% CI (%) N	29 (73) 56-85 40	1 (2) 0.062-13 41	1 (3) 0.068-14 37
	Visit 4	n (%) ≥ 1:8 95% CI (%) N	**40 (100)** 91-100 40	**38 (93)** 80-98 41	**28 (76)** 59-88 37
Y	**Visit 3**	n (%) ≥ 1:8 95% CI (%) N	29 (55) 40-68 53	0 0-7 54	0 0-9 38
	Visit 4	n (%) ≥ 1:8 95% CI (%) N	**53 (100)** 93-100 53	**36 (67)** 53-79 54	**24 (63)** 46-78 38

Source: Table 14.2.1.2.3. Individual subject results: Appendix 16.2.6.1.
Note: Visit 4 was performed 1 month after second vaccination (at visit 3).
CI = confidence interval; n = number of responders; N = number of patients with data at visits 3 and 4 per vaccine group (percentages were based on n/N).
[a] Group II vaccination 1: DtaP-Hib-IPV at 6 months

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines and Diagnostics S.r.l.	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient CRM_{197}-MenA conjugate; CRM_{197}-MenC conjugate; CRM_{197}-MenW conjugate; CRM_{197}-MenY conjugate		

Title of Study:

A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Compare the Safety of One Dose of Novartis Meningococcal ACWY Conjugate Vaccine with that of a Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Children 2 to 10 Years of Age

Protocol Number: V59P10

Investigators:

Ana Ceballos, MD; Daniel Stamboulian, MD; Silvia Gonzales Ayala, MD

Study Centers:

Centro de Desarrollo de Proyectos Avanzados CEDEPAP, Roma 1464, B Pueyrredon (X5000BJH), Cordoba, Argentina; FUNCEI – Fundacion Centro de Estudios Infectologicos, French 3085 (C1425AWK), Ciudad Autonoma de Buenos Aires, Argentina; Hospital de Pediatria “Sor Maria Ludovica”, Calle 14 N 1631, (1900) La Plata, Argentina.

Publication (reference): None

Study Period: (date of first enrollment): 24 MAY 06 (date of last completed): 21 MAR 07	**Phase of Development:** Phase 3

Objectives:

Immunogenicity Objectives

Primary Objective: To compare the immunogenicity of a single injection of Novartis MenACWY conjugate vaccine with the immunogenicity of a single injection of PS vaccine (Menomune), defined as the percentage of subjects with seroresponse in human serum bactericidal assay against *N meningitidis* serogroups A, C, W_{135}, and Y at 1 month after vaccination, when administered to healthy children 2 to 10 years of age. For the definition of seroresponse refer to section 4.

Secondary Objectives:

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Name of Active Ingredient CRM_{197}-MenA conjugate; CRM_{197}-MenC conjugate; CRM_{197}-MenW conjugate; CRM_{197}-MenY conjugate		

1. To compare the immunogenicity of a single injection of Novartis MenACWY conjugate vaccine and the immunogenicity of a single injection of PS vaccine (Menomune), defined as: (a) percentage of subjects with hSBA ≥ 1:4, (b) percentage of subjects with hSBA ≥ 1:8, and (c) hSBA geometric mean titers (GMTs) against *N meningitidis* serogroups A, C, W_{135}, and Y at 1 month after vaccination, when administered to healthy children 2 to 10 years of age.
2. To compare the immunogenicity of a single injection of Novartis MenACWY conjugate vaccine and the immunogenicity of a single injection of PS vaccine (Menomune), defined as: (a) percentage of subjects with hSBA ≥ 1:8, (b) percentage of subjects with hSBA ≥ 1:4, and (c) hSBA GMTs against *N meningitidis* serogroups A, C, W_{135}, and Y at day 181 after vaccination, when administered to healthy children 2 to 10 years of age.

Safety Objectives

Primary Objective: To compare the percentage of subjects presenting at least one severe (solicited) systemic reaction to the Novartis MenACWY conjugate vaccine with the percentage presenting at least one severe systemic reaction to the licensed meningococcal ACWY polysaccharide (PS) vaccine (Menomune) during the first 7 days (day 1 to 7) following a single injection administered to healthy children 2 to 10 years of age.

Secondary Objective: to describe and compare immediate hypersensitivity reactions; solicited adverse events (AEs), axillary temperature, AEs, and serious AEs.

Methodology:

A total of 1500 healthy children 2 to 10 years of age were randomly assigned to one of the two vaccine groups (MenACWY or Menomune) at a 2:1 ratio. The randomization was stratified by age with the following targets for the number of subjects to enroll per each age stratum: 750 children 2 to 5 years of age and 750 children 6 to 10 years of age. Blood samples were to be obtained from a subset of 75 subjects in each group and age stratum consenting to be included in the immunogenicity subset.

For a detailed description of the assessments made at each study visit refer to section 9.5.1. For the summary of the time and events, refer to Table 2-1.

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Name of Active Ingredient CRM_{197}-MenA conjugate; CRM_{197}-MenC conjugate; CRM_{197}-MenW conjugate; CRM_{197}-MenY conjugate		

Number of Subjects (planned and analyzed):

The target number for the enrolled subjects (1500) was achieved. The planned ratio 2:1, i.e. 1000 subjects in the MenACWY group and 500 subjects in the Menomune group was actually 950 subjects in the MenACWY group and 550 in the Menomune group. The age stratification target numbers (750 for each age group) were actually 716 subjects in the 2 to 5 age group and 784 subjects in the 6 to 10 age group. As planned, a total of 300 subjects (75 subjects from each of the 4 groups – 2 age groups and 2 vaccine groups) composed the immunogenicity subset, the only difference between planned and actual occurring in the MenACWY group, which had 74 subjects in the 2 to 5 age group and 76 subjects in the 2 to 10 age group. The above data are presented in Table 9.1-.1

Diagnosis and Main Criteria for Inclusion and Exclusion:

Individuals eligible for enrollment into this study were healthy male and female children 2 to 10 years of age, whose parents or legal guardians gave written informed consent at the time of enrollment and who were available for all visits and telephone calls scheduled for the study, who were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator, and who were up to date with primary course and booster vaccines (BCG and four doses of diphtheria-tetanus-pertussis vaccine [DTP], oral polio vaccine [OPV] or inactivated polio vaccine [IPV], *H influenzae* type b vaccine [Hib], measles-mumps-rubella vaccine [MMR], and hepatitis A or B, according to the vaccine calendar and subject age in Argentina). For the complete list of the exclusion criteria refer to section 9.3.2.

Test Product, Dose, Mode of Administration, Lot Number:

The investigational MenACWY conjugate vaccine (lot V79P39D1A, expiry date August 2007) was obtained by extemporaneous mixing, just before injection, of the lyophilized MenA component (MenA lot 006011, expiry date August 2007) to be resuspended with the liquid MenCWY component (MenCWY lot V79P39D1, expiry date May, 2008). After reconstitution, the MenACWY conjugate vaccine had the following antigen composition per 0.5 mL of injectable solution (for the full list of components, refer to section 9.4.2):

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Name of Active Ingredient CRM_{197}-MenA conjugate; CRM_{197}-MenC conjugate; CRM_{197}-MenW conjugate; CRM_{197}-MenY conjugate		

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA coniugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}

A single MenACWY conjugate vaccination was administered by intramuscular (IM) injection in the deltoid area of the arm.

Duration of Study:

Overall duration of the study was approximately 9 months, including 3 months of enrollment and 6 months of individual subject participation.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Licensed meningococcal ACWY PS vaccine Menomune, manufactured by Aventis Pasteur Inc., Swiftwater, PA, (lot UE322AA, expiry date 09 August 2006; lot UE471AA, expiry date 06 October 2006; lot C2582AA, expiry date April 2007) was supplied as a single injection (one vial of vaccine and one vial of diluent). The vaccine consisted of four meningococcal capsular polysaccharide serogroups (A, C, $W_{135,}$ and Y). After reconstitution with the liquid diluent, the PS vaccine had the following antigen composition (for the full list of components refer to section 9.4.2):

Composition	Quantity per 0.5 mL dose
Isolated product from each of groups A, C, W_{135} and Y	50 µg

A single injection of PS vaccine was administered by subcutaneous (SC) injection in the deltoid area of the arm.

Criteria for Evaluation:

Immunogenicity: The ability of MenACWY conjugate vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement hSBA will be measured using the following variables: percentage of subjects with hSBA seroresponse at day 29 (for the definition of seroresponse refer to section 4); percentage of subjects with hSBA $\geq$ 1:4 and hSBA $\geq$ 1:8 at day 29 and day

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181; geometric mean titers (GMTs), as measured by hSBA, at day 29 and day 181 and geometric mean ratio (GMR) of GMTs at day 29 over baseline (day 1).

Safety: The safety of the MenACWY conjugate vaccine was evaluated in terms of the percentage of subjects presenting at least one severe systemic reaction and by describing immediate hypersensitivity reactions following vaccination, local and systemic reactions and axillary temperature and adverse events (AEs) and serious adverse events (SAEs).

Statistical Methods:

The statistical methods that will be used to analyze immunogenicity are described in the protocol (section 16.1.1) and will be presented in CSR Part 2.

Safety of MenACWY conjugate vaccine was considered non-inferior to safety of PS vaccine if the upper limit of the two-sided 95% CI of the ratio (MenACWY conjugate vaccine group divided by PS vaccine group) of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (day 1 to day 7) after vaccination was less than 3. The null hypothesis associated with the safety objective was that the ratio (MenACWY conjugate vaccine group/PS vaccine group) of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (day 1 to day 7) after vaccination was at least 3. The other safety data were analyzed descriptively; refer to section 9.7 for further details.

Summary and Conclusions:

Immunogenicity results

This report refers to safety results only since serology analysis is still ongoing. As soon as the immunogenicity results are available, they will be presented in Part 2 to this report.

Safety results

A total of 1500 subjects were enrolled at a 2:1 ratio into the MenACWY (452 in the 2 to 5 year age stratification and 498 in the 6 to 10 year age stratification) and Menomune groups (264 in the 2 to 5 year age stratification and 286 in the 6 to 10 year age stratification).

Although the study was powered to test whether the percentages of subjects experiencing severe solicited systemic reactions (i.e., between days 1 to 7) to MenACWY were non-superior to those to Menomune, the observed percentage of

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subjects experiencing severe systemic reactions was very low (i.e., 1% [11 subjects] in the MenACWY group and <1% [1 subject] in the Menomune group). All severe systemic reactions were of limited duration (i.e., not more than 5 days with a median of 1 day) and resolved without sequelae. Although the primary objective was not met, the difference in the incidence rates of severe solicited systemic reactions has little clinical consequence.

The percentages of subjects reporting any solicited reaction in the two vaccine groups (47% and 52% for MenACWY and Menomune, respectively) and within age groups (2 to 5 year age group: 46% and 52%, respectively; in the 6 to 10 age group: 47% and 52%, respectively) were similar.

Overall, local reactions were reported by 34% of the MenACWY group and 41% of the Menomune group. The most frequently reported local reaction was pain (20% - 27% across age groups for MenACWY and 26% - 35% across age groups for Menomune). Most local reactions were experienced during the three days immediately following vaccination.

As different systemic reactions were solicited in the two different age groups (change in eating habits, sleepiness, irritability, vomiting, diarrhea, arthralgia, and headache for the 2 to 5 year age group, and arthralgia, headache, chills, nausea, malaise, and myalgia in the 6 to 10 year age group) no conclusion could be drawn regarding age-related trends. Most systemic reactions were experienced during the three days immediately following vaccination in both age groups and the percentages with reports of each were balanced between vaccination groups.

The majority of unsolicited reactions, as expected, occurred within the first 29 study days, generally reflecting the method of data collection (i.e., only SAEs and AEs requiring a physician visit/emergency room visit or resulting in early termination were to be reported after day 29). Overall, 21% of the MenACWY group reported unsolicited AEs during days 1 to 29 vs. 5% during days 29 to 181. Similar results were obtained for the Menomune group (16% and 6%, respectively). No possibly or probably related non-solicited reactions were reported after day 29. The possibly or probably related AEs reported in this study were caused by ongoing solicited reactions or other known side effects of conjugated vaccines.

One of the 10 SAEs (febrile convulsion, 12/010, MenACWY group) was assessed by

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the investigator as possibly related to the vaccine. The onset of the SAE was on study day 2, the event was of moderate severity, and it occurred in a subject with 2 prior episodes of febrile seizure. The episode of convulsion lasted less than 10 minutes and the subject was hospitalized for observation and discharged in good condition. The SAE was assessed as possibly related due to the temporal association to the vaccination. The seriousness criterion was hospitalization.

No deaths or AEs leading to discontinuation were reported in this study.

Conclusions

Overall MenACWY was safe and well tolerated in children aged 2 to 10 years. More subjects in the MenACWY group reported severe solicited systemic reactions than in the Menomune group; however incidence rates of these reactions were very low. Overall solicited reactions were of short duration, mostly mild or moderate in severity and were reported by similar percentages of subjects in MenACWY and Menomune group. One possibly related SAE was reported in a MenACWY recipient as assessed by temporal association.

Table 2-1 Time and Events

Study Day (window in days)	Screening (-14)	Day 1	Day 3 (+3) ☎	Day 8 (+3) ☎	Day 29 (+14)[a]	Day 181 (±15)[a]
Visit number		1			2	3
Procedures						
Obtain informed consent	X					
Inclusion/exclusion criteria	X					
Medical history and prior medications [b]	X					
Physical assessment	X	X			X [c]	X [c]
Obtain blood sample		X [c]			X [c]	X [c]
Administer study vaccine [d]		X				
Injection-site examination		X			X [c]	
Assess local and systemic reactions and body temperature [e]		X	X	X		
Concomitant medications		X	X	X	X	X
Adverse events [f]		X	X	X	X	X
Collect diary cards					X	
Collect worksheets						X
Study termination						X

Note: Day 1 is defined as the day of study vaccination.
[a] For subjects not included in the immunogenicity analysis, a phone call could replace the medical office visit.
[b] Includes vaccination history.
[c] Applicable to subjects included in the immunogenicity analysis.
[d] Vaccine administered after blood sample is obtained.
[e] Includes assessment of immediate hypersensitivity.
[f] From day 1 to 7, record and collect information regarding all AEs. From day 8 to 181, record and collect SAEs and information regarding any event requiring a physician visit/emergency room visit, and any event resulting in a subject's early termination from the study. From day 1 to 29, common childhood exanthematous diseases were also recorded.

Table 2-2 Incidence of Severe Systemic Reactions During Days 1 to 7

Systemic Reaction	Number (%), 95%CI of Subjects with Solicited Reaction		MenACWY/ Menomune Ratio, 95% CI	Primary Objective Criterion
	2 – 10 years MenACWY N=950	2 – 10 years Menomune N=550		Upper 95%CI limit< 3
Severe	11 (1%)	1 (< 1%)	**6.37 (0.82 – 49.2)**	**Not met**

Source: Table 14.3.1.1.2.3

Table 2-3 Overview of Local and Systemic Reactions, Overall and by Age Stratification

Type of Reaction	Number (%) of Subjects with Solicited Reactions					
	2 – 5 years		6 – 10 years		2 - 10 years	
	MenACWY N = 452	Menomune N = 264	MenACWY N = 498	Menomune N = 286	MenACWY N = 950	Menomune N = 550
Any reaction	209 (46%)	138 (52%)	235 (47%)	148 (52%)	444 (47%)	286 (52%)
Local reaction	138 (31%)	99 (38%)	189 (38%)	125 (44%)	327 (34%)	224 (41%)
Systemic reaction	130 (29%)	73 (28%)	119 (24%)	69 (24%)	249 (26%)	142 (26%)
Other reaction	69 (15%)	42 (16%)	69 (14%)	47 (16%)	138 (15%)	89 (16%)

Source: Table 14.3.1.1.2, Table 14.3.1.1.2.1, Table 14.3.1.1.2.2

Table 2-4 Overview of Unsolicited AEs, Days 1 to 29

Type of Reaction	Number (%) of Subjects with Unsolicited Adverse Events					
	2 – 5 years		6 – 10 years		2 – 10 years	
	MenACWY N = 452	Menomune N = 264	MenACWY N = 498	Menomune N = 286	MenACWY N = 950	Menomune N = 550
Any AE	115 (25%)	62 (23%)	81 (16%)	28 (10%)	196 (21%)	90 (16%)
Possibly or probably vaccine- related AE	10 (2%)	4 (2%)	6 (1%)	2 (1%)	16 (2%)	6 (1%)
Serious AEs[a]	3 subjects (< 1%) (12/010, 18/002, 30/074)		2 subjects (< 1%) (11/575, 20/568)		5 subjects (< 1%)	
AEs leading to discontinuation	0	0	0	0	0	0
Possibly or probably vaccine- related SAEs	1 subject (< 1%) (12/010)	0	0	0	1 subject (< 1%)	
Death	0	0	0	0	0	0

Source: Table 14.3.1.1.6, Table 14.3.1.1.7, Table 14.3.1.1.8, Table 14.3.1.1.11.1, Table 14.3.1.1.14.1, Table 14.3.2.2; [a] since serology analysis is still ongoing, the study is, where feasible, blinded at an individual level

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines & Diagnostics S.r.l. Via Fiorentina, 1 53100 Siena, Italy	Individual Study Table Referring to Part [ ] of the Dossier	*For National Authority Use Only*
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Name of Active Ingredient CRM_{197}-MenA conjugate CRM_{197}-MenC conjugate CRM_{197}-MenW conjugate CRM_{197}-MenY conjugate		
Title of Study: A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria and Acellular Pertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, or One Dose of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Subjects Aged 11 to 25 Years.		
Protocol Number:V59P11		
Investigators: Roberto Gasparini, MD; Sandro Cinquetti, MD; Michele Conversano, MD; Giovanni Gabutti, MD; Francesco Schioppa, MD; Claudio Vagnini, MD; Roberto Ieraci, MD; Gianni Bona, MD; Mario Cuccia, MD; Alessandro Maida, MD; Giuseppe Ferrera, MD; Nicola Casuccio, MD; Riccardo Matera, MD		
Study Centers: The 14 centers, all located in Italy, were: 01. Università degli studi di Genova, Dipartimento di Scienze della Salute, Genova; 02. Dipartimento di Prevenzione Azienda ULSS 7, Pieve di Soligo (TV); 03. Dipartimento di Prevenzione SISP Massafra, V.le Magna Grecia, Massafra; 04. Location 1: Dipartimento di Medicina Clinica e Sperimentale -Sezione di Igiene e Medicina Preventiva, Ferrara, Location 2: Servizio di Igiene Pubblica, Ferrara; 05. Dipartimento di Medicina e Scienze dell'Invecchiamento, Università G. D'Annunzio, Chieti; 06. Ufficio Igiene e Sanità Pubblica di Lanciano, ASL Lanciano, Lanciano; 07. Azienda USL di Modena, Distretto di Pavullo, Modena; 08. Travel Clinic, ASL RM/E, Roma; 09. Ospedale Maggiore della Carità, Clinica Pediatrica, Novara; 10. Dipartimento di Prevenzione, ASL CT, Catania; 11. Istituto di Igiene e Medicina Preventiva, Sassari; 12. AUSL 7 Ragusa, Ragusa; 13. AUSL 6 PA, Dipartimento di Prevenzione - Servizio di epidemiologia, Palermo; 14. ASL BAT 1, Servizio di Igiene Pubblica, Andria.		
Publication (reference): None		

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Study Period First subject enrolled: 18 APR 2006 Last subject completed: 08 MAY 2007	**Phase of Development:** Phase 3

Objectives

Immunogenicity Objectives

Primary

To demonstrate that the immunogenicity of a single injection of Tdap vaccine, separately but concomitantly administered with Meningococcal ACWY Conjugate Vaccine (MenACWY), is not inferior to that of a single injection of Tdap vaccine, concomitantly administered with saline placebo.

Secondary

- To compare the immunogenicity of a single injection of Tdap vaccine when given separately but concomitantly with MenACWY, to that of a single injection of Tdap vaccine, concomitantly administered with saline placebo.
- To evaluate the immunogenicity of a single injection of MenACWY vaccine, separately but concomitantly administered with Tdap, and that of a single injection of MenACWY vaccine, concomitantly administered with saline placebo.

Safety Objectives: To compare the safety profile following a single injection of MenACWY administered with Tdap vaccine to that of either Tdap administered with saline placebo or MenACWY administered with saline placebo in healthy subjects 11 to 25 years of age, defined as percentage and number of subjects with: immediate hypersensitivity reactions following vaccination; local and systemic reactions (i.e., solicited adverse events [AEs]) and axillary temperature reported during the period day 1 to 7 after vaccination; unsolicited AEs reported during the period day 1 to 29 after vaccination; medically significant AEs reported during the period day 30 to 181 after vaccination; and serious adverse events (SAEs) reported during the whole duration of the study.

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Methodology: Subjects were randomized at a 1:1:1 ratio to receive concomitant administrations of either Tdap and MenACWY vaccines, or Tdap vaccine with saline placebo, or MenACWY with saline placebo. Subjects were administered each of the concomitant vaccines in different arms. Blood was drawn before vaccination, at day 1 and after vaccination, at day 29. From day 30 to day 181, only safety was collected.

For the summary of the time and events, refer to Table 2-1. For the detailed description of the study events, including "Medical History and Safety Assessments", refer to section 9.5.1

Number of Subjects (planned and analyzed): A total of 999 evaluable subjects (333 for each vaccination group) were planned to be enrolled. A total of 1072 subjects were enrolled and randomized to receive Tdap vaccine and MenACWY vaccine (333 subjects planned, 361 actually enrolled), Tdap vaccine and saline placebo (333 subjects planned, 354 actually enrolled), or MenACWY and saline placebo (333 subjects planned, 357 actually enrolled). All subjects except for 25 subjects with major protocol deviations were included in the immunogenicity analyses. Titers against meningococcal serogroups A, C, W, and Y were planned to be determined by human serum bactericidal assay (hSBA) in a randomly selected subset of 300 subjects (150 from each of the two MenACWY-containing groups) (245 actually analyzed). Information on the planned and actually analyzed subjects is also presented in Table 9.1-1 and section 11.2.

Diagnosis and Main Criteria for Inclusion and Exclusion

Inclusion Criteria: 11 to 25 years of age: if 11 to 17 years of age, they were subjects who gave their written assent and whose parents or legal guardians gave written informed consent at the time of enrollment, or, if 18 to 25 years of age, were mentally competent and able to give the written informed consent prior to study entry; were available for all visits and telephone calls scheduled for the study, were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator, and had received the primary immunization with a vaccine containing DT or Tdap antigens and a T, Td, or Tdap booster injection at least 5 years prior to study entry.

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Exclusion criteria are given in section 9.3.2.

Test Product, Dose, Mode of Administration, Lot Number

1) MenACWY conjugate vaccine, lot V79P39D1, expiry date: August 2007

The investigational MenACWY vaccine was obtained by extemporaneous mixing, just before injection, of the lyophilized MenA component to be resuspended with the liquid MenCWY component. After reconstitution, the MenACWY vaccine had the following antigen content per 0.5 mL injectable solution, which was administered by intramuscular (IM) injection in the deltoid area (for the full list of components refer to section 9.4.2):

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}

2) Tdap vaccine (GSK Boostrix), lot AC37B015AB, expiry date: July 2007

One 0.5 mL injection of Boostrix vaccine was administered by IM injection in the deltoid area. For the full list of components refer to section 9.4.2.

Composition	Quantity per 0.5 mL dose
Diphtheria Toxoid	2.5 Lf
Tetanus Toxoid	5 Lf
Pertactin	2.5 µg
FHA	8 µg
Inactivated PT	8 µg

Duration of Study: Approximately 12 months, including 6 months of enrollment and 6 months of individual subject participation

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Reference Therapy, Dose, Mode of Administration, Lot Number:
Saline Placebo, lot (b) (4). One 0.5 mL injection of saline placebo was administered by IM injection in the deltoid area.

Composition	Quantity per 0.5 mL dose
Sodium chloride	4.5 mg
WFI	Qs to 0.5 mL

Criteria for Evaluation

Immunogenicty

Primary: percentages of subjects, 1 month after injection, with antibody levels (as determined by ELISA) against: diphtheria toxin ≥ 1 IU/mL; tetanus toxin ≥ 1 IU/mL; seroresponse (4-fold increase) against pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN).

Secondary:

- percentages of subjects with antibody levels, as determined by ELISA, against: diphtheria and tetanus toxins ≥ 0.1 IU/mL at 1 month postvaccination; antidiphtheria, antitetanus, anti-PT, anti-FHA, and anti-PRN geometric mean antibody concentration (GMC) at baseline and at 1 month after vaccination; GMC increase (GMR) from baseline at 1 month after vaccination.
- percentages of subjects with hSBA seroresponse against *N meningitidis* serogroup A, C, W, and Y at 1 month after vaccination (for the definition of seroresponse to MenACWY, refer to section 4); percentage of subjects with hSBA titer ≥ 1:4 and hSBA titer ≥ 1:8 against *N meningitidis* serogroups A, C, W, and Y at 1 month after vaccination; hSBA geometric mean titer (GMT) against *N meningitidis* serogroups A, C, W, and Y at baseline and at 1 month after vaccination, and hSBA GMRs from baseline at 1 month after vaccination.

Safety: The numbers and percentages with reported solicited and unsolicited AEs.

Statistical Methods: The immunogenicity of Tdap when given concomitantly with MenACWY was considered noninferior to that of Tdap when administered with saline

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placebo, if for all five antigens (diphtheria, tetanus, PT, FHA and PRN) the lower limit of the two-sided 95% confidence interval (CI) for the [(Tdap + MenACWY) minus (Tdap + saline)] difference in the response percentage was greater than -10%. The null hypothesis associated with the primary immunogenicity objective was that for at least one antigen, the underlying percent response in the group receiving Tdap and MenACWY was at least 10% lower than the one in the group receiving Tdap and saline placebo [i.e., (Tdap + MenACWY) minus (Tdap + saline) ≤ -10%]. Other immunogenicity and all safety objectives, both for Tdap and MenACWY, were evaluated descriptively.

Summary and Conclusions:

Immunogenicity results

A total of 1072 subjects were enrolled and randomized at a 1:1:1 ratio to receive Tdap + MenACWY (361 subjects), Tdap + saline (354 subjects), or MenACWY + saline (357 subjects). The PP population of each vaccine group comprised 97% to 98% of the enrolled population. Baseline and other demographic characteristics were generally balanced between the vaccine groups.

The primary objective of the study was to show that the immune response to diphtheria toxin (% of subjects with antibody titer ≥ 1.0 IU/mL), tetanus toxin (% of subjects with antibody titer ≥ 1.0 IU/mL), pertussis toxin (4-fold increase), filamentous hemagglutinin (4-fold increase), and pertactin (4-fold increase) when Tdap was administered concomitantly with MenACWY was not inferior to that induced when Tdap was administered concomitantly with saline placebo. Although the primary objective was achieved for diphtheria, tetanus and filamentous hemagglutinin, it was not met for pertussis toxin or pertactin since the lower limit of the two-sided 95% CIs on the difference in the percentage of responders was below -10% (Table. 11.4.1.1-1). The clinical relevance of this finding is not clear since the correlates of protections for pertussis are not established. The noninferiority assumption for pertussis was based on the percentages of subjects with at least a 4-fold rise following vaccination with Boostrix. Failure to show noninferiority for two of the pertussis antigens may have been influenced by lower than expected immune responses (as compared to the GMCs

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reported in the Package Insert) to Boostrix in this study.

In the secondary immunogenicity analyses, one month after vaccination, nearly all subjects (99% to 100%) had antibody concentrations ≥ 0.1 IU/mL against diphtheria and tetanus toxins. There was a greater increase in GMCs against diphtheria when Tdap was administered with MenACWY (day 29/ day 1 GMR: 72) than with saline placebo (day 29/ day 1 GMR: 22). Tdap induced similarly robust antibody responses against tetanus, PT, FHA, and PRN regardless of the concomitant vaccine used.

In a subset of 245 subjects tested for MenACWY immunogenicity, increases in GMTs, as determined by human serum bactericidal assay (hSBA), induced by MenACWY when administered concomitantly with either Tdap or saline placebo were evaluated. Similar responses to MenACWY were observed for serogroups C, W, and Y (day 29/ day 1 GMRs: 22 vs. 23; 6.9 vs. 8.09; 14 vs. 14) regardless of the concomitant vaccine or placebo administration scheme applied. However, GMTs against serogroup A increased 16-fold (95% CI: 11, 33) after MenACWY was administered concomitantly with Tdap and 23-fold (95% CI: 16, 33) when administered concomitantly with saline placebo. The percentages of subjects with hSBA titers ≥ 1:4 and ≥ 1:8 were similar. For both of these criteria, the percentages were similar between the MenACWY + Tdap and MenACWY + saline groups; for serogroups C, W, and Y they ranged between 88% and 97%, while for serogroup A they ranged between 74% and 83%. With the exception of serogroup A, where all nine subjects with baseline titers ≥ 4 seroresponded (3 in the Tdap+MenACWY group and 6 in the MenACWY group), generally there was a higher response (4-fold increase) rate in subjects with baseline titer <4 in both vaccination groups; however the sample sizes in the by baseline titer analyses were relatively small (N = 37 to 87 subjects across the C, W, and Y serogroups).

In conclusion, the immune response against diphtheria toxin, tetanus toxin, and filamentous hemagglutinin after Tdap administered concomitantly with MenACWY was noninferior to that induced by Tdap administered concomitantly with saline placebo. Robust immune response was observed to all Tdap antigens (including pertussis toxin and pertactin) regardless of whether a concomitant vaccine was administered. Generally, the immune responses induced by MenACWY against any

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serogroup were not influenced by whether the concomitant vaccine was Tdap or saline placebo.

Safety results

A total of 1072 subjects were enrolled at a 1:1:1 ratio to receive either Tdap administered concomitantly with Men ACWY (Tdap + MenACWY), Tdap administered concomitantly with saline placebo (Tdap + saline), or MenACWY administered concomitantly with saline placebo (MenACWY + saline). A total of 1069 subjects were vaccinated (359 received MenACWY + Tdap, 353 Tdap + saline, and 357 MenACWY + saline).

The percentages of subjects in the MenACWY + saline group reporting any solicited AE, solicited local AEs, and solicited systemic AEs during days 1 to 7 were lower than in the Tdap + MenACWY or Tdap + saline groups (any, 65% vs. 82% to 88%; local, 50% vs. 77% to 80%; systemic, 48% vs. 55% to 57%).

Although pain was the most frequent injection site reaction to all three vaccinations given in the study, the percentage of subjects reporting pain to the saline placebo was lower than for Tdap or MenACWY (12% to 16% placebo vs. 63% to 70% Tdap and 23% to 32% MenACWY). Severe pain, although highest after Tdap injection (5% to 8% vs. 1% to 3% in the other groups) was relatively infrequent and of short duration. Most local reactions were experienced during the first three days postvaccination, since no more than 1% increase was observed in the percentages reporting each local reaction in days 1 to 7 versus days 1 to 3.

Similar percentages of subjects reported systemic reactions among the three vaccine groups, both overall and by age stratum (11 to 18 years and 19 to 25 years of age). The most commonly reported systemic reactions were headache (31% to 36%) and myalgia (22% to 36%). Severe headache was reported by 3% to 7% across vaccine groups, and severe myalgia by 3% to 4%. No subject experienced a fever equal to or higher than 40°C. Most systemic reactions were experienced during the first three days postvaccination.

The percentage of subjects reporting unsolicited AEs necessitating a physician's visit and/or leading to emergency room visit and/or resulting in premature withdrawal from

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the study was balanced among the vaccine groups during the period day 1 to 29 (9% to 13%, none of which reported an AE leading to withdrawal). During the period day 30 to 181, unsolicited medically significant AEs were reported for 10% to 12% of the vaccine groups. No possibly or probably related unsolicited AE was reported after day 29. In total, twenty subjects (nineteen in the 11 to 18 years age stratum and 1 in the 19 to 25 years age stratum) reported at least possibly related unsolicited AEs. Of these, nineteen subjects reported possibly or probably related unsolicited AEs with onset between days 1 and 7. Only one episode of pyrexia and another of headache were reported between days 8 and 29. Pyrexia was the most commonly experienced possibly or probably related unsolicited AE (1 to 3 subjects per vaccine group). No severe possibly or probably related unsolicited AE was reported.

No deaths occurred during this study. A total of three SAEs, all assessed as not related to the study vaccine, were reported during the study (heat stroke, nephrolithiasis, upper abdominal pain). No AEs leading to discontinuation were reported in this study.

Conclusions

When Tdap was administered concomitantly with MenACWY, immune responses to PT and PRN, but not to diphtheria, tetanus or FHA, were lower than when Tdap was administered concomitantly with saline placebo. However, as serologic correlates of protection for pertussis are not established, the clinical relevance of this finding is not clear. In addition, pertussis immune responses, as measured by GMCs, were robust against all antigens regardless of whether Tdap was administered with MenACWY or saline placebo. Results from the exploratory analysis showed that the immune response of MenACWY when given concomitantly with Tdap was comparable to the immune response of MenACWY given with saline placebo. When MenACWY was administered concomitantly with Tdap, no significant enhancement of reactogenicity was observed relative to each vaccine given with saline placebo.

Compared directly to Tdap, MenACWY was well tolerated with lower reactogenicity profile. No unexpected unsolicited or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

Table 2-1 Time and Events

Study day (window)	**day 1**	**day 3 (+3) ☎**	**day 8 (+3) ☎**	**day 29 (+15)**	**day 181 (±15) ☎**
Visit number **Procedures**	**1**			**2**	
Obtain informed assent and consent	X				
Medical history	X				
Physical assessment	X			X	
Obtain blood sample	X			X	
Administer study vaccine(s) and/or placebo	X				
Injection-site examination	X			X	
Assess local and systemic reactions; all adverse events[a] and axillary temperature	X	X	X		
Prior and concomitant medications	X	X	X	X	X
Adverse events[a]			X	X	
Medically significant adverse events[a]				X	X
Serious adverse events	X	X	X	X	X
Study termination					X

Note: day 1 is defined as the day of study vaccination.
[a] Refer to Table 9.5.1-1

Table 2-2 **Primary Immunogenicity Objective: Percentage of Subjects in the Tdap-containing groups with Antidiphtheria and Antitetanus Titer ≥ 1.0 IU/mL and at Least 4-fold Increase for PT, FHA and PRN**

Day	Variable	Tdap+ MenACWY % (95% CI)	Tdap + saline % (95% CI)	Vaccine difference (95% CI)
Diphtheria		**N=350**	**N=345**	
Day 1	≥ 1.0 IU/mL	4% (2%, 7%)	5% (3%, 7%)	0% (-4%, 3%)
Day 29	≥ 1.0 IU/mL	94% (91%, 96%)	85% (80%, 88%)	9% (5%, 14%)
Tetanus		**N=350**	**N=345**	
Day 1	≥ 1.0 IU/mL	25% (20%, 30%)	36% (31%, 42%)	-11% (-18%, 5%)
Day 29	≥ 1.0 IU/mL	100% (99%, 100%)	99% (98%, 100%)	1% (-1%, 2%)
PT		**N=286**	**N=287**	
Day 29	4-fold increase	76% (70%, 80%)	81% (76%, 85%)	-5% (-12%, 1%)
FHA		**N=286**	**N=287**	
Day 29	4-fold increase	83% (78%, 87%)	86% (82%, 90%)	-3% (-9%, 3%)
PRN		**N=285**	**N=287**	
Day 29	4-fold increase	84% (79%, 88%)	91% (87%, 94%)	-7% (-13%, -2%)

Source: Table 14.2.1.2.1, Table 14.2.1.4.1, Table 14.2.1.5.1, Table 14.2.1.6.1, Table 14.2.1.7.1

Table 2-3 ELISA GMCs at Day 1 and Day 29 and GMRs at Day 29/Day 1 for Diphtheria, Tetanus, PT, FHA, and PRN in the Tdap-containing groups

Day	Variable	Tdap + MenACWY GMC/GMR (95% CI)	Tdap + saline GMC/GMR (95% CI)	Vaccine ratio (95% CI)
Diphtheria		**N=350**	**N=345**	
Day 1	GMC	0.11 (0.085, 0.14)	0.12 (0.096, 0.16)	0.88 (0.75, 1.04)
Day 29	GMC	7.96 (6.19, 10)	2.77 (2.15, 3.57)	2.87 (2.42, 3.42)
	GMR (day 29/1)	72 (58, 91)	22 (18, 28)	3.26 (2.82, 3.76)
Tetanus		**N=350**	**N=345**	
Day 1	GMC	0.62 (0.5, 0.76)	0.75 (0.61, 0.92)	0.82 (0.72, 0.94)
Day 29	GMC	12 (9.84, 14)	15 (13, 18)	0.78 (0.69, 0.88)
	GMR (day 29/1)	19 (14, 25)	20 (15, 26)	0.95 (0.82, 1.1)
PT		**N=286**	**N=287**	
Day 1	GMC	2.68 (1.97, 3.66)	2.85 (2.1, 3.86)	0.93 (0.66, 1.32)
Day 29	GMC	62 (52, 74)	79 (66, 93)	0.79 (0.62, 1)
	GMR (day 29/1)	23 (18, 30)	28 (21, 36)	0.84 (0.63, 1.11)
FHA		**N=286**	**N=287**	
Day 1	GMC	15 (13, 18)	17 (14, 20)	0.9 (0.76, 1.07)
Day 29	GMC	186 (165, 209)	219 (194, 246)	0.85 (0.74, 0.98)
	GMR (day 29/1)	12 (10, 14)	13 (11, 15)	0.93 (0.78, 1.11)
PRN		**N=285**	**N=287**	
Day 1	GMC	6.45 (5.18, 8.03)	8.7 (7.01, 11)	0.74 (0.58, 0.94)
Day 29	GMC	157 (131, 189)	254 (211, 304)	0.62 (0.5, 0.77)
	GMR (day 29/1)	24 (20, 30)	29 (24, 35)	0.83 (0.67, 1.03

Source: Table 14.2.1.11.1, Table 14.2.1.12.1, Table 14.2.1.13.1

Table 2-4 Overview of Solicited AEs, Days 1 to 7, Overall and by Age Stratum

Type of Reaction	Number (%) of Subjects with Solicited Adverse Events (Reactions)								
	11 – 18 years			19 – 25 years			11 – 25 years		
	Tdap + MenACWY N=313	Tdap + saline N=315	MenACWY + saline N=316	Tdap + MenACWY N=46	Tdap + saline N=38	MenACWY + saline N=41	Tdap + MenACWY N=359	Tdap + saline N=353	MenACWY + saline N=357
Any reaction	263 (84%)	277 (88%)	206 (65%)	33 (72%)	32 (84%)	26 (63%)	296 (82%)	309 (88%)	232 (65%)
Local reaction	245 (78%)	253 (80%)	161 (51%)	33 (72%)	29 (76%)	18 (44%)	278 (77%)	282 (80%)	179 (50%)
Systemic reaction	178 (57%)	183 (58%)	150 (47%)	20 (43%)	19 (50%)	21 (51%)	198 (55%)	202 (57%)	171 (48%)
Other reaction	37 (12%)	34 (11%)	26 (8%)	5 (11%)	5 (13%)	7 (17%)	42 (12%)	39 (11%)	33 (9%)

Source: Table 14.3.1.1.2.1, Table 14.3.1.1.2.2, Table 14.3.1.1.2

Table 2-5 Overview of Unsolicited AEs, Days 1 to 29, Overall and by Age Stratum

Type of Reaction	Number (%) of Subjects with Unsolicited Adverse Events								
	11 – 18 years			19 – 25 years			11 – 25 years		
	Tdap + MenACWY N=313	Tdap + saline N=315	MenACWY + saline N=316	Tdap + MenACWY N=46	Tdap + saline N=38	MenACWY + saline N=41	Tdap + MenACWY N=359	Tdap + saline N=353	MenACWY + saline N=357
Any AE	37 (12%)	28 (9%)	38 (12%)	6 (13%)	3 (8%)	10 (24%)	43 (12%)	31 (9%)	48 (13%)
Poss/prob related AE	8 (3%)	5 (2%)	6 (2%)	0	1 (3%)	0	8 (2%)	6 (2%)	6 (2%)
SAEs	0	0	0	0	0	0	0	0	0
AEs leading to discont	0	0	0	0	0	0	0	0	0
Poss/prob related SAE	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0

Source: Table 14.3.1.1.11.1, Table 14.3.1.1.11.5, Table 14.3.1.1.14.1, Table 14.3.1.1.14.5, Table 14.3.2.2, Table 14.3.1.1.7, Table 14.3.1.1.7.1, Table 14.3.1.1.6, Table 14.3.1.1.8, Appendix 16.2.7.5

Table 2-6 Overview of Unsolicited AEs, Days 30 to 181, Overall and by Age Stratum

Type of Reaction	Number (%) of Subjects with Unsolicited Adverse Events								
	11 – 18 years			19 – 25 years			11 – 25 years		
	Tdap + MenACWY N=313	Tdap + saline N=315	MenACWY + saline N=316	Tdap + MenACWY N=46	Tdap + saline N=38	MenACWY + saline N=41	Tdap + MenACWY N=359	Tdap + saline N=353	MenACWY + saline N=357
Any AE	50 (16%)	39 (12%)	53 (17%)	7 (15%)	7 (18%)	8 (20%)	42 (12%)	36 (10%)	39 (11%)
Poss/prob related AE	0	0	0	0	0	0	0	0	0
SAEs	1 (<1%)	2 (1%)	0	0	0	0	1 (<1%)	2 (1%)	0
AEs leading to discont	0	0	0	0	0	0	0	0	0
Poss/prob related SAE	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0

Source: Table 14.3.1.1.11.4, Table 14.3.1.1.11.6, Table 14.3.1.1.14.4, Table 14.3.1.1.14.6, Table 14.3.2.2, Table 14.3.1.1.7, Table 14.3.1.1.7.1, Table 14.3.1.1.6, Table 14.3.1.1.8, Appendix 16.2.7.5

2.0 SYNOPSIS

Name of Sponsor: Novartis Vaccines & Diagnostics, Inc. 4560 Horton Street, Emeryville, CA 94608-2916	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product: Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient: MenA, MenC, MenW, and MenY, each conjugated to CRM_{197}		

Title of Study: A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age

Protocol Number: V59P13

Coordinating Investigator: Lisa Jackson, MD MPH

Study Centers: 44 centers in the US

Publication (reference): None

Study Period: First subject enrolled: 01 MAR 07 Last subject completed: 16 JAN 08	**Phase of Development:** Phase 3

Objectives:

Immunogenicity

Primary Objectives (all at 1 month after a single injection)

- To show consistency of immune response for three lots of MenACWY, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 18 years of age);
- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra™, defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy adolescents 11 to 18 years of age);
- To compare the immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of

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subjects with seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy adults 19 to 55 years of age).

For the definition of seroresponse refer to section 4 of this report.

Secondary Objectives (all at 1 month after a single injection)

- To assess consistency of immune response for three lots of MenACWY, as measured by the percentage of subjects with seroresponse, hSBA titer ≥ 1:4 and ≥ 1:8, directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy adolescents 11 to 18 years of age);
- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55 years of age);
- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8, directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55 years of age);
- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, as measured by hSBA GMTs directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55 years of age).

Safety

Primary Objective

To compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY to the percentage of subjects presenting at least one severe systemic reaction to Menactra during the first 7 days (days 1 to 7) following a single injection administered to healthy subjects (11 to 55 years of age).

Secondary Objective

To describe and compare the safety profile following a single injection of MenACWY (3 lots combined) to that following a single injection of Menactra administered to

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healthy adolescents or adults (11 to 55 years of age) defined as the percentage and number of subjects with: immediate hypersensitivity reactions (within 30 minutes) following vaccination; local and systemic reactions during the period study day 1 to 7; adverse events (AEs) reported during the period study day 1 to 29; medically significant AEs reported during the period study day 30 to 180; serious adverse events (SAEs) reported from study day 1 to 180.

Methodology:

A total of 3539 subjects 11 to 55 years of age were randomized at a 1:1:1:1 ratio to one of four vaccine groups (MenACWY Lot 1, Lot 2, Lot 3, or Menactra). Randomization was stratified by center and age so that 2180 adolescents (11 to 18 years of age), 413 adults (19 to 34 years of age) and 946 adults (35 to 55 years of age) were enrolled. Subjects were administered either MenACWY or Menactra intramuscularly (IM) by an unblinded study vaccine administrator. The subjects were blinded to the study vaccine given. All safety follow-up performed by the investigator and study staff was also blinded. Blood was drawn before vaccination, at day 1, and after vaccination, at day 29 (window:+14 days). From day 29 to day 180 only safety was collected.

For the summary of the time and events, refer to Table 2-1. For the detailed description of the study events, including "Medical History and Safety Assessments", refer to section 9.5.1 of this report and section 6.5.5 of the study protocol.

Number of Subjects (planned and analyzed):

Approximately 3432 subjects 11 to 55 years of age were planned to be randomly assigned to receive either one injection of one of the three MenACWY lots or one injection of Menactra. A total of 3539 subjects were actually enrolled in the study. The table below shows the planned and actual number of subjects enrolled.

Planned and Actual Enrollment

Vaccine Group	Subjects enrolled (planned) and actual	Subjects enrolled (planned) and actual		
		11-18	19-34	35-55
MenACWY Lot 1	(2574) 2663	(525) 548	(100) 104	(233) 235
MenACWY Lot 2		(525) 548	(100) 98	(233) 241

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Menactra	(858) 876	(525) 540	(100) 105	(233) 231

The number of subjects planned for immunogenicity testing in each age group for each serogroup is provided is section 9.1. The number of subjects actually tested in each age group for each serogroup is provided in section 11.1.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Individuals eligible for enrollment in this study were male and female individuals 11 to 55 years of age inclusive who, after the nature of the study was explained, either gave written assent and/or for whom the parent or legal guardian provided written informed consent (11 to 17 years of age), or provided written informed consent (18 to 55 years of age); who were available for all visits and telephone calls scheduled for the study; and who were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator.

For the list of exclusion criteria refer to section 9.3.2.

Test Product, Dose, Mode of Administration, Lot Number:

The investigational Novartis MenACWY conjugate vaccine was obtained by extemporaneous mixing, just before injection, of the lyophilized MenA component (lot numbers Z008011, Z009011, and Z010011 for the Lot 1, Lot 2, and Lot 3 groups, respectively) with the MenCWY full liquid vaccine (lot numbers Z79P40I1, Z79P41I1, and Z79P42I1, respectively).

After reconstitution, MenACWY had the following antigen composition per 0.5 mL of injectable solution which was administered by IM injection in the left deltoid area (for the full list of components refer to section 9.4.2 of this report):

Composition	**Quantity per 0.5 mL dose**
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}

Duration of Study: The planned duration of the study was approximately 9 months overall, including 3 months for enrollment and 6 months of individual subject

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participation. The actual enrollment period was approximately 5 months.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Licensed meningococcal ACWY polysaccharide-protein conjugate vaccine Menactra (manufactured by Aventis Pasteur Inc., Swiftwater, PA) was supplied as a single 0.5 mL injection (administered by IM injection in the left deltoid area) formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. For the full list of components refer to section 9.4.2 of this report.

Criteria for Evaluation:

Immunogenicity

Primary

- Immunogenicity of the 3 lots of MenACWY was considered equivalent if for each serogroup and each pair of vaccine lots, the two-sided 95% confidence interval (CI) of the ratio of the GMTs 1 month after the vaccination was within the interval [0.50, 2.0]. (The null hypothesis associated with this objective was that the 95% CI for the ratio would fall outside the interval [0.50, 2.0]).
- Immunogenicity of MenACWY (3 lots combined) was considered noninferior to the immunogenicity of Menactra in the 11 to 18 yoa and 19 to 55 yoa groups, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (MenACWY minus Menactra) was greater than -10%. (The null hypothesis associated with this objective was that the lower limit of the two-sided 95% CI for the difference would be ≤ -10%). A MenACWY serogroup was considered to have a statistically significant higher immune response compared with that same serogroup of Menactra if the lower limit of the two-sided 95% CI around the difference in percentage of seroresponders (MenACWY minus Menactra) was greater than 0, i.e., the CI did not include zero. The combined hypothesis testing for noninferiority and statistical superiority did not require any adjustment for multiplicity.

The success criterion for this study was a composite based upon all three co-primary objectives: lot-to-lot consistency for the three MenACWY lots and seroresponse

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noninferiority of MenACWY as compared with Menactra for the 11 to 18 and 19 to 55 yoa groups. Novartis was to consider this study a success if all 20 of the analyses (4 serogroups times 3 pairs of lots for the ratio of GMTs plus 4 serogroups times 2 age groups for the MenACWY vs. Menactra seroresponse comparison) met the criteria specifically identified for the respective endpoints.

Secondary

- Immunogenicity of the three lots of MenACWY was considered equivalent if for each serogroup and each pair of vaccine lots, the two-sided 95% CI on the difference in proportions of responders (seroresponse, hSBA titer ≥ 1:8, or hSBA titer ≥ 1:4) was within the interval [-10%, 10%]. (The null hypotheses associated with these objectives [seroresponse, hSBA titer ≥ 1:8, and hSBA titer ≥ 1:4] were that the two-sided 95% CI would fall outside the interval [-10%, 10%]).
- Immunogenicity of MenACWY (3 lots combined) was considered noninferior to the immunogenicity of Menactra, in the 11 to 55 years group, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with: (a) seroresponse; (b) hSBA ≥ 1:8 (or hSBA ≥ 1:4) for that serogroup (MenACWY minus Menactra) was greater than -10%. (The null hypotheses associated with these two objectives were that the lower limit of the two-sided 95% CI for the difference would be ≤ -10%). The superiority of MenACWY in comparison to Menactra was also assessed for any given serogroup using the same statistical criterion as for the primary objective.
- Immunogenicity response of MenACWY (3 lots combined) was considered noninferior to the immunogenicity of Menactra, in the 11 to 55 yoa group, if the lower limit of the two-sided 95% CI around the ratio of hSBA GMTs between MenACWY and Menactra (MenACWY/Menactra) at 1 month after vaccination was above 0.5. (The null hypothesis associated with this objective was that the lower limit of the two-sided 95% CI for the ratio would be ≤ 0.5).

Safety

The measures of safety used in this study consisted of local and systemic reactions and other adverse events.

MenACWY was considered noninferior to Menactra with respect to severe systemic

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reactions if the upper limit of the 2-sided 95% CI of the difference ($P_{MenACWY}$ minus $P_{Menactra}$) was less than 6%, where $P_{MenACWY}$ and $P_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (day 1 to day 7) after vaccination with MenACWY (3 lots combined) and Menactra, respectively. (The null hypothesis associated with this objective was that it would be $\geq$ 6%).

Statistical Methods:

The statistical null hypotheses associated with each of the primary and secondary immunogenicity objectives and with the primary safety objective are presented in the Criteria for Evaluation section of this Synopsis. Secondary safety objectives were evaluated descriptively. Detailed statistical methods are presented in section 9.7 of this report.

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Summary and Conclusions:

Immunogenicity results

A total of 3539 subjects were enrolled and randomized at a 1:1:1:1 ratio to receive one injection of MenACWY (lot 1, lot 2, or lot 3) or Menactra. A total of 2649 subjects were administered MenACWY and 875 Menactra. The PP population of both vaccine groups was 96% of the enrolled population. Baseline and other demographic characteristics were similar between the vaccine groups, both in the 11 to 18 yoa MenACWY population (analyzed for lot-to-lot consistency) and in the overall enrolled population.

All three primary immunogenicity objectives, all measured at 1 month after a single injection of vaccine, were met:

- In the 11 to 18 MenACWY age group, for all four serogroups and all three pairs of vaccine lots, the two-sided 95% CI on the ratio of the GMTs (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) was within the interval [0.5, 2.0] set as the success criterion for the primary lot-to-lot consistency objective (Table 11.4.1.1-1, Figure 11.4.1.1-1). The null hypothesis associated with the primary lot-to-lot consistency objective was rejected.
- In the 11 to 18 age group, the lower limit of the 95% CI around the difference of the percentage of overall seroresponders (MenACWY minus Menactra) was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups A, W, and Y (Table 11.4.1.1-2). The null hypothesis associated with the primary noninferiority objective for this age stratum was rejected.
- In the 19 to 55 age group, the lower limit of the 95% CI around the difference of the percentage of overall seroresponders (MenACWY minus Menactra) was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups C, W, and Y (Table 11.4.1.1-2). The null hypothesis associated with the primary noninferiority objective for this age stratum was rejected.

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The two secondary immunogenicity lot-to-lot consistency objectives were not met:

- The two-sided 95% CI of the difference in the proportions of seroresponders was within the interval [-10%, 10%], set as the success criterion for the secondary lot-to-lot consistency objective, for all three pairs of MenACWY vaccine lot groups (Lot 1 minus Lot 2, Lot 1 minus Lot 3, and Lot 2 minus Lot 3) for serogroup C (statistical power 80%), while it was outside this range for at least one pair of MenACWY lots for serogroups A (statistical power 49%), W (statistical power 49%), and Y (statistical power less than 39%, Table 11.4.1.2-1). The null hypothesis associated with the secondary seroresponse consistency objective was not rejected.
- The two-sided 95% CI on the difference in the proportion of subjects with hSBA titer ≥ 1:8 at day 29 was within the interval [-10%, 10%] for each of the three pairs of MenACWY vaccine lots for serogroups C, W, and Y (statistical power greater than 90%) but it was outside this range for one of the three pairs of MenACWY lots for serogroup A (statistical power 49%, Table 11.4.1.2-1). The null hypothesis associated with the lot-to-lot-consistency hSBA ≥1:8 objective was not rejected.

All three secondary immunogenicity noninferiority objectives were met:

- In the 11 to 55 age group, the lower limit of the two-sided 95% CI around the difference in the percentages of seroresponders between the MenACWY and Menactra groups was greater than -10% (noninferiority criterion) for all four serogroups and it was greater than 0% (superiority criterion) for serogroups C, W, and Y (Table 11.4.1.2-2). The null hypothesis associated with the seroresponse immunogenicity noninferiority objective was rejected.
- In the 11 to 55 age group, the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with hSBA titer ≥ 1:8 was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups W and Y (Table 11.4.1.2-2). The null hypothesis associated with the hSBA titer ≥ 1:8 noninferiority objective was rejected.

The lower limit of the two-sided 95% CI around the ratio of hSBA GMTs between the MenACWY and Menactra groups was above 0.5 (noninferiority criterion) for all four serogroups (Table 11.4.1.2-3). The null hypothesis associated with the hSBA GMT

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Name of Active Ingredient: MenA, MenC, MenW, and MenY, each conjugated to CRM_{197}		

noninferiority was rejected.

Safety results

A total of 3539 subjects were enrolled and randomized at a 1:1:1:1 ratio to receive either MenACWY lot 1, lot 2, lot 3, or Menactra. A total of 3524 subjects were vaccinated (2649 received MenACWY and 875 Menactra).

The primary safety objective, to compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY to that observed in the Menactra group during the first 7 days following a single injection administered to healthy subjects 11 to 55 years of age, was met: the upper limit of the 95% CI of the vaccine group difference was 2%, below the criterion set by the noninferiority assumption, i.e., <6%.

The percentages of subjects reporting solicited AEs and local solicited AEs were lower in the MenACWY group than in the Menactra group (solicited AEs: 62% vs. 67%, respectively; local solicited AEs: 48% vs. 53%, respectively), while they were similar for the systemic solicited AEs and other indicators of reactogenicity (systemic: 41% vs. 40%, respectively; other reactions: 21% in both vaccine groups).

The most frequently reported local solicited AE was pain, which was reported by significantly lower percentages of subjects in the MenACWY group than in the Menactra group during days 1 to 7 (42% vs. 48%, respectively, $P < .001$) and during days 1 to 3 (41% vs. 48%, respectively, $P < .001$), while it was slightly more frequent during days 4 to 7 (12% vs. 9%, respectively, $P = .012$), indicating a possibly longer duration of pain in the MenACWY group. Severe pain was reported by similar percentages in the two vaccine groups (0.7% and 0.8% in the MenACWY and Menactra groups, respectively). Induration and erythema > 50 mm were more often reported in the MenACWY group, including 8 subjects (0.3%; all MenACWY recipients) with induration > 100 mm. All local reactions were transient; the median duration of all severe local reactions was similar in the MenACWY and Menactra groups (range 2 to 4 days).

Most local reactions were experienced during the first three days postvaccination since

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no more than a 1% increase in the overall population was observed in the percentages reporting each of the local reactions during days 1 to 7 vs. days 1 to 3 in either of the two vaccine groups.

Similar percentages of subjects reported systemic solicited AEs in the MenACWY and Menactra groups (41% and 40%, respectively, *P* = .32). In both vaccine groups, the most commonly reported systemic solicited AEs were headache (28% and 27%, respectively), myalgia (17% in both vaccine groups), and malaise (11% in both vaccine groups). Severe headache was reported by 2% and 1%, respectively, while severe myalgia and malaise were reported by 1% in both vaccine groups. Most systemic solicited AEs were reported in the first three days postvaccination.

The percentages of subjects reporting unsolicited AEs requiring a physician's visit, emergency room visit, or premature withdrawal were similar between the MenACWY and Menactra groups during the day 1 to day 29 period (19% and 20%, respectively, none of which reported an AE leading to withdrawal). During the day 30 to day 180 period, unsolicited medically significant AEs were reported for 10% and 7% in the MenACWY and Menactra groups, respectively. No possibly or probably related unsolicited AE was reported after day 29.

In total, 207 subjects reported at least one possibly related unsolicited AEs (6% in both vaccine groups). The most commonly experienced possibly or probably related unsolicited AEs were injection site erythema and injection site pruritis, reported each by 21 subjects (0.8%) in the MenACWY group and 2 subjects (0.2%) in the Menactra group. The other most commonly reported possibly or probably related unsolicited AE reported was headache, reported by 14 subjects (0.5%) in the MenACWY group and 4 subjects (0.5%) in the Menactra group.

No death occurred during this study. A total of 28 subjects reported SAEs, all assessed as not related to the study vaccines. No AE leading to discontinuation was reported in this study.

Conclusions

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The first of the primary objectives demonstrated consistency among the three MenACWY lots for all four serogroups (i.e., for all three pair-wise comparisons, the two-sided 95% CI of the ratio of the GMTs [Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3] was within the interval [0.5, 2.0]).

The other two co-primary objectives showed that the seroresponse to MenACWY was noninferior to that of Menactra for all four serogroups both in the 11 to 18 and 19 to 55 age stratifications (i.e., the lower limit of the two-sided 95% CI around the difference in the percentages of seroresponders was greater than -10%). In addition, seroresponse to MenACWY was demonstrated to be superior (i.e., two-sided 95% CI was greater than 0%) to that of Menactra for serogroups A, W, and Y in the 11 to 18 age group and for serogroups C, W, and Y in the 19 to 55 age group.

All 20 protocol-specified analyses performed for the primary objectives (four serogroups times three pairs of lots for GMT ratios, plus four serogroups times two age groups for the MenACWY vs. Menactra comparison) met the protocol-specified criteria for noninferiority or lot-to-lot consistency.

The primary safety objective demonstrated that MenACWY was noninferior to Menactra in terms of severe systemic reactions(i.e., the upper limit of the two-sided 95% CI of the difference in the percentage of subjects experiencing at least one severe reaction was below 6%).

Both study vaccines were well tolerated with similar reactogenicity profiles. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

Table 2-1 Time and Events

Visit Number	**1**	☎	**2**	☎
Study Day (window)	Day 1	Day 3 (Study days 3 – 5)	Day 29 (Study days 29 – 43)	Day 180 (Study days 165 – 195)
Obtain Informed consent/assent	X			
Medical History	X			
Physical Assessment[a]	X		X	
Obtain Blood Sample	X		X	
Administer Study Vaccine[b]	X			
Injection-site Examination	X [b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications[c, d]	X		X	X
Serious Adverse Events[e]	X	X	X	X
Study Termination				X

Note: day 1 was defined as day of study vaccination.
[a] The physical assessments at visit 1 (study day 1) was performed by a study physician or designee.
[b] All subjects were observed in the clinic for 30 minutes after vaccination.
[c] Collected data on concomitant medications prescription and non prescription through the first 7 days.
[d] Collected data on concomitant medications (prescriptions only) from day 8 through day 180.
[e] Collected information regarding any SAE or any event resulting in a subject's early termination at any time during the subject's study participation. A 6-month follow up call was made to assess the occurrence of SAEs and significant medical events (Refer to Table 9.5.1-1 for the relevant definitions)

Table 2-2 Primary Lot to Lot Consistency Objective: hSBA GMT Vaccine Group Ratios at Day 29, Ages 11 to 18 Years, PP Population

		Day 29 GMT vaccine group ratios (95% CI)
A[a]	Lot 1 / Lot 2	0.89 (0.68, 1.16)
	Lot 1 / Lot 3	0.95 (0.73, 1.23)
	Lot 2 / Lot 3	1.06 (0.81, 1.38)
C[b]	Lot 1 / Lot 2	1.33 (1, 1.77)
	Lot 1 / Lot 3	1.2 (0.9, 1.6)
	Lot 2 / Lot 3	0.9 (0.68, 1.2)
W[c]	Lot 1 / Lot 2	0.79 (0.63, 0.97)
	Lot 1 / Lot 3	1.06 (0.86, 1.31)
	Lot 2 / Lot 3	1.35 (1.09, 1.67)
Y[d]	Lot 1 / Lot 2	0.79 (0.61, 1.02)
	Lot 1 / Lot 3	0.91 (0.7, 1.18)
	Lot 2 / Lot 3	1.16 (0.89, 1.5)

Source: Table 14.2.1.1.1
[a] serogroup A: Lot 1 N=359, Lot 2 N= 357, Lot 3=359
[b] serogroup C: Lot 1 N=499, Lot 2 N=493, Lot 3 N=491
[c] serogroup W: Lot 1 N=340, Lot 2 N=341, Lot 3 N=343
[d] serogroup Y: Lot 1 N=345, Lot 2 N=345, Lot 3 N=346

Table 2-3 Primary Immunogenicity Objective: Percentage of Seroresponders at Day 29, Ages 11 to 18 and 19 to 55, PP Population

			11-18			19-55		
			MenACWY	**Menactra**	**Vaccine Group Difference** (95% CI)	**MenACWY**	**Menactra**	**Vaccine Group Difference** (95% CI)
A	Baseline titer	<1:4	75% 780/1039	66% 230/347	9% (3%, 15%)	67% 582/875	67% 191/283	-1% (-7%, 5%)
		≥ 1:4	58% 21/36	67% 8/12	-8% (-35%, 24%)	70% 62/88	71% 27/38	-1% (-17%, 18%)
	Overall		75% 801/1075	66% 238/359	**8%** **(3%, 14%)**	67% 644/963	68% 218/321	**-1%** **(-7%, 5%)**
C	Baseline titer	<1:4	79% 771/977	79% 260/331	0% (-5%, 6%)	71% 425/596	62% 133/214	9% (2%, 17%)
		≥ 1:4	68% 345/506	62% 105/170	6% (-2%, 15%)	61% 223/365	51% 53/104	10% (-1%, 21%)
	Overall		75% 1116/1483	73% 365/501	**2%** **(-2%, 7%)**	67% 648/961	58% 186/318	**9%** **(3%, 15%)**
W	Baseline titer	<1:4	94% 570/609	83% 150/180	10% (5%, 17%)	82% 131/160	71% 67/94	11% (0%, 22%)
		≥ 1:4	47% 193/415	28% 30/108	19% (9%, 28%)	35% 112/324	26% 52/198	8% (0%, 16%)
	Overall		75% 763/1024	63% 180/288	**12%** **(6%, 18%)**	50% 243/484	41% 119/292	**9%** **(2%, 17%)**
Y	Baseline titer	<1:4	81% 510/630	54% 95/176	27% (19%, 35%)	66% 173/263	52% 83/160	14% (4%, 23%)
		≥ 1:4	47% 192/406	22% 26/118	25% (16%, 34%)	45% 108/240	27% 39/146	18% (9%, 28%)
	Overall		68% 702/1036	41% 121/294	**27%** **(20%, 33%)**	56% 281/503	40% 122/306	**16%** **(9%, 23%)**

Source: Table 14.2.1.2.1, 14.2.1.3.1

Table 2-4 Primary Safety Objective: Percentage of Subjects With at Least One Severe Systemic Reaction, Days 1 to 7, Age 11 to 55

Systemic Reaction	Number (%), 95%CI of Subjects with Solicited Reaction		MenACWY minus Menactra Vaccine Group Difference, 95% CI	Primary Safety Objective Criterion
	11 – 55 years MenACWY N=2649	11 – 55 years Menactra N=875		Upper 95%CI limit **<6%**
Severe	94 (4%)	24 (3%)	**1% (-1%, 2%)**	**Met**

Source: Table 14.3.1.1.2.1

Table 2-5 Overview of Solicited AEs, Days 1 to 7, Age 11 to 55

Type of Reaction	Number (%) of Subjects with Solicited Reaction	
	MenACWY N=2649	Menactra N=875
Any reaction	1649 (62%)	585 (67%)
Local reaction	1275 (48%)	467 (53%)
Systemic reaction	1086 (41%)	350 (40%)
Other reaction[a]	555 (21%)	183 (21%)

Source: Table 14.3.1.1.2
[a] analgesic/antipyretic medications used and stayed at home due to vaccination

Table 2-6 Overview of Unsolicited AEs, Days 1 to 29, Age 11 to 55

Type of Reaction	Number (%) of Subjects with Unsolicited Adverse Event	
	MenACWY N=2649	Menactra N=875
Any AE	509 (19%)	174 (20%)
Possibly probably related AEs	156 (6%)	51 (6%)
SAEs	4 (0.2%)	2 (0.2%)
AEs leading to discontinuation	0	0
Possibly probably related SAEs	0	0
Death	0	0

Source: Table 14.3.1.1.11.1, Table 14.3.1.1.14.1, Table 14.3.2.2, Table 14.3.1.1.8, Table 14.3.1.1.6

Table 2-7 Overview of Unsolicited AEs, Days 30 to 180, Age 11 to 55

Type of Reaction	Number (%) of Subjects with Unsolicited Adverse Event	
	MenACWY N=2622	Menactra N=864
Any AE	253 (10%)	60 (7%)
Possibly probably related AEs	0	0
SAEs	19 (0.7%)	3 (0.3%)
AEs leading to discontinuation	0	0
Possibly probably related SAEs	0	0
Death	0	0

Source: Table 14.3.1.1.11.2, Table 14.3.1.1.14.2, Table 14.3.2.2, Table 14.3.1.1.8, Table 14.3.1.1.6

2.0 SYNOPSIS

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Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient MenA, MenC, MenW, and MenY, each conjugated to CRM_{197}		

Title of Study:

A Phase 3, Randomized, Observer-blind, Controlled, Multicenter Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune™) when One Dose is Administered to Healthy Subjects 56-65 Years of Age

Protocol Number: V59P17

Coordinating Investigator: Daniel Stamboulián, MD

Study Centers:

- Centro de Estudios Infectologicos, Carabobo 825, Flores, Buenos Aires, Argentina C1406DGI;
- Corporación Científica Pediatrica, Calle 9 #50'25 Oficina 405, Cali, Colombia;
- Centro de Investigación, Cientifica Alejandra Valencia, Avenida 9 116-20, Consultorio 806, Fundacion Santa Fe, Bogota, Colombia

Publication (reference): None.

Study Period:	**Phase of Development:**
First subject enrolled: 23 May 2007 Last subject completed: 26 Feb 2008	3

Objectives:

Note: Only safety results are presented in this Clinical Study Report (CSR). The immunogenicity results will be discussed in a supplemental addendum to the CSR.

Primary Objective

Safety

- To compare the percentage of subjects presenting at least one severe systemic reaction to meningococcal ACWY conjugate vaccine (MenACWY) with the percentage presenting at least one severe systemic reaction to Menactra during the

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first 7 days (days 1 to 7) following a single dose administered to healthy subjects (19 to 55 years of age).

Secondary Objectives

Immunogenicity

- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse, human Serum Bactericidal Activity (hSBA) ≥ 1:4 or ≥ 1:8 directed against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, as measured by serum bactericidal activity geometric mean titer (GMT) response using human complement (hSBA GMTs) directed against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menomune, defined as percentage of subjects with hSBA ≥ 1:4 or ≥ 1:8 or a seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menomune, as measured by hSBA GMTs directed against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

Safety

- To describe and compare the percentages of subjects in the MenACWY and Menactra vaccine groups and the MenACWY and Menomune vaccine groups when administered to healthy adults aged 19 to 55 years and aged 56 to 65 years, respectively, in terms of:
  - Immediate hypersensitivity reactions (within 30 minutes) following vaccination,
  - Local and systemic reactions during study days 1 to 7,
  - Adverse events (AEs) reported during study days 1 to 29,

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- Medically significant AEs reported during study days 30 to 180,
- Serious adverse events (SAEs) reported over the 6-month follow-up period from study day 1 to 180.

Methodology:

This was a phase 3, observer-blind, multicenter, randomized, controlled study in healthy subjects (19 to 65 years of age). Approximately 2500 healthy subjects 19 to 55 years of age were to be randomly assigned to receive either MenACWY or Menactra. Immunogenicity testing was carried out for the first 200 subjects of the 19 to 34 years of age subgroup and for the first 200 subjects of the 35 to 55 years subgroup; these subjects were randomized in a 1:1 ratio. The remaining subjects in both age groups were randomized in a 2:1 ratio. Subjects in the 56 to 65 year subgroup were randomized in a 2:1 ratio (MenACWY:Menomune), and the initial 225 subjects were tested for immunogenicity. After vaccination, the subjects were monitored in the clinic for 30 minutes to assess any signs or symptoms of anaphylaxis, local injection site reactions, and systemic reactions. An independent, external Data Monitoring Committee (DMC) was established to monitor safety by reviewing scheduled analyses.

Number of Subjects (planned and analyzed):

Approximately 2500 healthy subjects 19 to 55 years of age were to be randomly assigned to receive either MenACWY or Menactra. A total of 450 subjects were to be randomly assigned in the 56 to 65 years of age subgroup. A total of 2831 subjects were actually enrolled in the study. The table below shows the actual and planned number of subjects enrolled.

Planned and Actual Enrollment

Vaccine Group	**Subjects enrolled: Actual** (Planned)		
	Total Subjects	**19-55 years**	**56-65 years**
MenACWY (Group I)	**1823** (1900)	**1606** (1600)	**217**(300)
Menactra (Group II)	**899** (900)	**899** (900)	—
Menomune (Group III)	**109** (150)	—	**109** (150)
Total	**2831** (2950)	**2505** (2500)	**326** (450)

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Individuals eligible for enrollment in this study were those who were 19 to 65 years of age inclusive and who, after the nature of the study had been explained, had provided written informed consent; who were available for all visits and telephone calls scheduled for the study; and who were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator.

Subjects not eligible to be enrolled in the study were those who (main exclusion criteria): were unwilling or unable to give written informed consent to participate in the study; were perceived to be unreliable or unavailable for the duration of the study period; had a previous or suspected disease caused by *N meningitidis*; had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* infection within 60 days prior to enrollment; were previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of Outer Membrane Protein [OMP]-containing *Haemophilus influenzae* type b [Hib] vaccines was permitted); had received any investigational agents or vaccines within 90 days prior to enrollment or expected to receive an investigational agent or vaccine prior to the completion of the study; had received any licensed vaccines within 1 month prior to enrollment or for whom receipt of a licensed vaccine was anticipated within 1 month after vaccination (Exception: Influenza vaccine could have been administered up to 15 days prior to study vaccination and at least 15 days after study vaccination); had received a live viral vaccine within 60 days prior to enrollment; or had experienced a significant acute or chronic infection within the 7 days prior to enrollment (for example, requiring systemic antibiotic treatment or antiviral therapy) or fever (≥ 38°C) within 3 days prior to enrollment.

Test Product, Dose, Mode of Administration, Lot Number:

The Novartis MenACWY conjugate vaccine (lot number: Z79P41I1) was administered intramuscularly (IM) in the left upper deltoid area. After reconstitution, the MenACWY vaccine composition per 0.5 mL of injectable solution was as follows:

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MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
Water for injection	

Duration of Study:

Approximately 9 months overall: 3 months of enrollment and 6 months of individual subject participation

Reference Therapy, Dose, Mode of Administration, Lot Number:

Menactra

Licensed meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine Menactra™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) was supplied as a single 0.5 mL dose formulated in sodium-phosphate-buffered, isotonic, sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier (lot number: U1948AA). Menactra was administered IM in the left upper deltoid area.

Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide	4 µg
Serogroup C polysaccharide	4 µg
Serogroup Y polysaccharide	4 µg

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Serogroup W135 polysaccharide	4 µg
Diphtheria toxoid protein total (each polysaccharide is conjugated to diphtheria toxoid)	48 µg
Sodium phosphate	(b) (4)
Sodium chloride	

Menomune

Licensed Menomune™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) was supplied as two vials: one vial containing a single dose of lyophilized meningococcal capsular polysaccharide serogroups Men A, C, Y, and W-135 combined component and the second vial containing the diluent. The contents of the lyophilized Menomune vial were to be reconstituted with the diluent. Menomune was administered by subcutaneous injections in the left upper arm (lot number: UE986AB). After reconstitution, Menomune composition per 0.5 mL of injectable solution was as follows:

Menomune Composition

Composition	**Quantity per 0.5 mL dose**
Serogroup A polysaccharide	50 µg
Serogroup C polysaccharide	50 µg
Serogroup W-135 polysaccharide	50 µg
Serogroup Y polysaccharide	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: water for injection	qs to 0.5 mL

Criteria for Evaluation:

Immunogenicity:

The ability of MenACWY vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (hSBA) was measured. Additional assays to further characterize the immune response to vaccine components were allowed by protocol and may have been performed.

Safety:

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Safety was evaluated in terms of the percentage of subjects presenting at least one severe systemic reaction during the first 7 days after vaccination and by describing immediate hypersensitivity reactions following vaccination, local and systemic reactions, body temperature, AEs, and SAEs.

Statistical Methods:

Safety analysis:

The null hypothesis associated with the safety objective was that the upper limit of the 2-sided 95% confidence interval (CI) for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra groups ($P_{MenACWY}$ - $P_{Menactra}$) was ≥ 6%.

MenACWY conjugate vaccine was considered noninferior to Menactra vaccine with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference (MenACWY vaccine group minus Menactra vaccine group) of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (days 1 to 7) after vaccination was < 6%.

Summary and Conclusions:

Immunogenicity results

Not applicable. As serology analyses are still ongoing, only safety results are presented in this report. The immunogenicity results will be presented in a supplemental addendum to the CSR.

Safety results

A total of 2831 subjects were enrolled and randomized in the study. Overall, 2489 subjects (1600 MenACWY and 889 Menactra) were vaccinated in the 19 to 55 years age group while 326 subjects (217 MenACWY and 109 Menomune) were vaccinated in the 56 to 65 years age group.

The primary safety objective, to compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY with the percentage presenting at least one severe systemic reaction to Menactra during the first 7 days (days 1 to 7) following a single dose administered to healthy subjects 19 to 55 years of age, was met: the upper limit of the 95% CI of the vaccine group difference was 3%, which was below the

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criterion set by the noninferiority assumption, i.e., < 6%.

The percentages of subjects reporting solicited AEs (i.e., local and systemic reactions collected during the 7 days after vaccination) were balanced between the vaccination groups and within each age group, with 60% MenACWY subjects and 64% Menactra subjects experiencing any reaction in the 19 to 55 age group and 57% of MenACWY and Menomune subjects in the 56 to 65 age group. Overall, the solicited reactions were short in duration and the median duration of all solicited reactions was similar in all vaccine groups. The solicited reactions were mostly mild or moderate in severity.

Any local injection site reactions (pain, erythema, and induration) were reported at similar frequencies in both age groups, with 46% of MenACWY and 50% of Menactra subjects in the 19 to 55 years age group compared to 43% of MenACWY and 40% of Menomune subjects in the 56 to 65 years age group. No obvious differences in any local injection site reactions were seen between the vaccine groups. In both age groups, most local reactions were reported during the 3 days immediately following the vaccination. However, the incidence of pain during days 4 to 7 in the 56 to 65 years age group was statistically significantly lower for the Menomune group (5%) compared to MenACWY (20%) ($P = .001$). The difference in reporting of pain was most probably due to differences in the vaccine formulations; in particular, the contribution of the diphtheria-component of MenACWY in the form of CRM, which is a common vaccine antigen to which previous exposure in this population is likely.

The incidence rates of systemic reactions were balanced between vaccination groups and within each age stratification (19 to 55 years: 39% MenACWY and 43% Menactra; 56 to 65 years: 39% MenACWY and 40% Menomune). No clinically meaningful differences were seen between the vaccine groups. Most systemic reactions were reported during the 3 days immediately following the vaccination in both age groups.

The majority of unsolicited reactions, as expected, occurred within the first 29 study days, generally reflecting the method of data collection (i.e., only SAEs and AEs requiring a physician visit/emergency room visit or resulting in early termination were to be reported after day 29). In the 19 to 55 years age group, the percentage of subjects experiencing any unsolicited AEs during days 1 to 29 was balanced between the vaccination groups (19% MenACWY and 21% Menactra). Whereas in the 56 to 65 years age group, the percentage of subjects experiencing any unsolicited AEs was

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slightly higher for MenACWY (25%) compared to Menomune (15%). During days 30 to 180, the percentage of subjects reporting any unsolicited AEs was balanced between the vaccine groups and both age group (19 to 55 years: 7% MenACWY and 8% Menactra; 56 to 65 years: 12% MenACWY and Menomune). Only a small percentage of subjects reported possibly or probably related unsolicited AEs during days 1 to 29.

The incidence rate for reported SAEs was generally low in all vaccine groups and age groups. Overall, 21 SAEs were reported during the study, 12 in the MenACWY group, eight in the Menactra group and one in the Menomune group. One SAE (spontaneous abortion) was considered possibly related to the study vaccine by the investigator.

There was one death (hypovolaemic shock) reported during this study which was not considered related to the vaccine.

Conclusions

Overall, MenACWY was safe and well tolerated in subjects aged 19 to 65 years. The percentages of subjects reporting solicited AEs (i.e., local and systemic reactions collected during the 7 days after vaccination) were comparable between the vaccine groups within each age group (MenACWY vs. Menactra in the 19 to 55 years of age group and MenACWY vs. Menomune in the 56 to 65 years of age group). Overall, the solicited reactions were of short duration with the median duration of all solicited reactions being similar in all vaccine groups. The solicited reactions were mostly mild or moderate in severity. One SAE was reported in a MenACWY recipient that was considered possibly related to the study vaccine.

Table 2-1: Time and Events

Visit Number	**1**	☎	**2**	☎
Study day (time window)	**Day 1**	**Day 3 (days 3 – 5)**	**Day 29 (days 29 - 43)**	**Day 180 (days 152 – 208)**
Obtain Informed consent	X			
Medical History	X			
Physical Assessment[a]	X		X	
Obtain Blood Sample[e]	X		X	
Administer Study Vaccine[b]	X			
Injection-site Examination	X[b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications[c]	X		X	X
Serious Adverse Events[d]	X	X	X	X
Adverse Events[f]	X		X	X
Study Termination				X

Note: Day 1 is defined as day of study vaccination.
[a] The physical examinations at visits 1 (day 1) were performed by a study physician.
[b] All subjects were observed in the clinic for 30 minutes after vaccination.
[c] Data on concomitant medications prescription and non-prescription were collected throughout the first 7 days. Data on concomitant medications (prescription only) for treatment of reportable AEs were collected throughout the entire study.
[d] Information regarding any SAE or any event resulting in a subject's early termination any time during the subject's study participation was collected. A 6-month follow up call was made to assess the occurrence of SAEs and medically significant AEs. Home or office visits could have been substituted at the discretion of the investigator.
[e] For subjects in the immunogenicity subset only.
[f] See Table 9.5.1-1

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines & Diagnostics S.r.l. Via Fiorentina, 1 53100 Siena, Italy	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
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Title of Study: A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL) in Healthy Adolescents

Protocol Number: V59P18

Investigators: Adriano Arguedas, MD

Study Centers: Instituto de Atencion Pediatrica, San Jose, Costa Rica

Publication (reference): None

Study Period: First subject enrolled: 19 JUL 2007 Last subject completed visit 3: 09 FEB 08	**Phase of Development:** Phase 3

Objectives:

Immunogenicity Objectives

Primary

- Demonstrate that the immune response to MenACWY, as measured by the percentage of hSBA seroresponders, when given concomitantly with Tdap and HPV is not inferior to the immune response when MenACWY is administered alone. For the definition of seroresponse refer to section 4 of this report.
- Demonstrate that the immune response to MenACWY, as measured by the percentage of hSBA seroresponders, when given one month after Tdap, is not inferior to the immune response when MenACWY is administered alone.
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, and anti-PRN GMCs, when given concomitantly with MenACWY

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and HPV, is not inferior to the immune response when Tdap is administered alone.

Secondary

- Demonstrate that the immune response to the HPV vaccine given concomitantly with MenACWY and Tdap is not inferior to the immune response to HPV administered alone. (Since the study is still ongoing and HPV results are not yet available, they are not presented in this interim report and will be presented in the final CSR at study completion.)
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, anti-PRN GMCs, when administered one month after MenACWY is not inferior to the immune response to Tdap administered alone.
- Assess the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥1:4, when given: (a) concomitantly with Tdap and HPV; and (b) when given one month after Tdap.
- Assess the antidiphtheria and antitetanus GMCs and the percentage of subjects with a 4-fold rise in antibody titer over baseline against PT, FHA, PRN.

Safety Objectives

- Assess the safety profile following a single injection of MenACWY given alone 1 month after Tdap, compared with the safety profile following a single injection of MenACWY given alone 1 month before Tdap.
- Assess the safety profile following a single injection of MenACWY given alone or concomitantly with Tdap and HPV vaccine.
- Assess the safety profile following a single injection of HPV given alone or concomitantly with Tdap and MenACWY (not presented in this interim CSR).

Methodology: Subjects were randomized at a 1:1:1 ratio to receive:

- MenACWY concomitantly with Tdap and HPV at study month 0 followed by two

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injections of HPV at month 2 and 6 (MenACWY+Tdap+HPV group);

- MenACWY at study month 0 followed by one injection of Tdap at month 1, followed by three injections of HPV at months 2, 4, and 8 (MenACWY → Tdap group);
- Tdap at month 0 followed by one injection of MenACWY at month 1, followed by three injections of HPV at months 2, 4, and 8 (Tdap → MenACWY group).

Randomization was stratified by gender and age group (11 to 14 years of age and 15 to 18 years of age). Study vaccines were administered and blood samples were obtained as summarized in the table below:

	MenACWY + Tdap + HPV	**MenACWY → Tdap**	**Tdap → MenACWY**
Month 0 (day 1, visit 1)	Serology [M, T, H] MenACWY+Tdap+HPV	Serology [M] MenACWY	Serology [T] Tdap
Month 1 (day 31, visit 2)	Serology [M, T]	Serology [M, T,] Tdap	Serology [M, T] MenACWY
Month 2 (day 61, visit 3)	HPV	Serology [T, H] HPV	Serology [M, H] HPV
Month 4 (day 121, visit 4)	--	HPV	HPV
Month 6 (day 181, visit 5)	HPV	--	--
Month 7 (day 211, visit 6)	Serology [H]	--	--
Month 8 (day 241, visit 7)	--	HPV	HPV
Monht 9 (day 271, visit 8)	--	Serology [H]	Serology [H]

[M] analyzed for MenACWY; [T] analyzed for Tdap; [H] analyzed for HPV

The results presented in this interim CSR are the final immunogenicity results for MenACWY and Tdap (sera obtained up to visit 3) and interim safety results (safety data collected up to visit 3).

Number of Subjects (planned and analyzed): A total of 1620 subjects were planned to be enrolled in the study, 540 in each of the three vaccine groups. A total of 1620 subjects were actually enrolled and vaccinated, as summarized in the table below:

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Planned and Actual Enrollment and Analyses

Enrolled and vaccinated (planned)		**MenACWY + Tdap + HPV** 540 (540)	**MenACWY → Tdap** 541 (540)	**Tdap → MenACWY** 539 (540)
ACWY	MITT	508 (94%)	508 (94%)	484 (90%)
	PP	500 (93%)	490 (91%)	464 (86%)
Tdap	MITT	503 (93%)	484 (89%)	498 (92%)
	PP	495 (92%)	459 (85%)	487 (90%)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Male or female individuals 11 to 18 years of age who gave their written assent and, if applicable, whose parents or legal guardians gave written informed consent at the time of enrollment, were virgins (both male and female) with no intention of becoming sexually active during the study period, were available for all visits and telephone calls scheduled for the study, were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator, and who were properly vaccinated against diphtheria, tetanus, pertussis (i.e., who had received five doses of pediatric DTP/DTaP before their seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose was not needed)

For the list of exclusion criteria refer to section 9.3.2.

Test Product, Dose, Mode of Administration, Lot Number:

MenACWY conjugate vaccine, lot Z79P40I1, expiry date: Feb 2008. A 0.5 mL injectable solution, administered by intramuscular injection (IM) in the right deltoid area, contained 10µg MenA and 5µg of each of MenC, MenW, and Men Y, each conjugated to CRM_{197}. For the full list of components refer to section 9.4.2.

Duration of Study: The planned duration of the study is approximately 11 months overall, including two months for enrollment and 9 months of individual subject participation.

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Reference Therapy, Dose, Mode of Administration, Lot Number:

1) HPV vaccine (Merck & Co. GARDASIL), lot 0515U, expiry date: 10 Feb 2010. A 0.5 mL injectable solution was administered IM in the upper anterolateral area of the thigh. For the list of components refer to section 9.4.2.

2) Tdap vaccine (GSK US-licensed Boostrix, available commercial lots). A 0.5 mL injectable solution was administered IM in the left deltoid area. For the list of components refer to section 9.4.2.

Criteria for Evaluation:

Immunogenicity

Since HPV results from this ongoing study are not yet available and will be presented in the final CSR, the criteria listed below are only for the MenACWY and Tdap endpoint analyses.

Primary:

- Concomitant noninferiority for MenACWY: lower limit of the two-sided 95% CI of the difference in the percentages of seroresponders for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone) to be >-10%;
- Concomitant noninferiority for Tdap:
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY+HPV+Tdap minus Tdap alone) to be >-10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, anti-PRN GMCs (MenACWY+HPV+Tdap / Tdap alone) to be >0.67.
- Sequential noninferiority for MenACWY: lower limit of the two-sided 95% CI of the difference in the percentages of seroresponders for each serogroup (Tdap → MenACWY minus MenACWY alone) to be >-10%.

Secondary

- Concomitant and sequential noninferiority for MenACWY (criteria non pre-specified in the study protocol):

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- lower limit of the two-sided 95% CI of the difference in the percentages for hSBA ≥ 1:8 and ≥ 1:4 for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone) to be >-10%;
- lower limit of the two-sided 95% CI for the vaccine group ratio of the hSBA GMTs (MenACWY+HPV+Tdap / MenACWY alone) to be >0.5.

- Sequential noninferiority for Tdap
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY → Tdap minus Tdap alone) to be >-10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, and anti-PRN GMCs (MenACWY → Tdap / Tdap alone) to be >0.67.

The antidiphtheria and antitetanus GMCs and the percentage of subjects with at least a 4-fold rise in antibody titer over baseline against PT, FHA, and PRN, secondary endpoints for the assessment of both concomitant and sequential administration of Tdap, were evaluated descriptively

Safety
The measures of safety used in this study consisted of solicited local and systemic reactions and other unsolicited adverse events.

Statistical Methods:
Detailed statistical methods, including the statistical null hypotheses associated with each of the primary and secondary noninferiority immunogenicity objectives are presented in section 9.7 of this report. Safety objectives were evaluated descriptively.

Summary and Conclusions:
Immunogenicity results
A total of 1620 subjects were enrolled and randomized at a 1:1:1 ratio to one of the three vaccine groups (see table in the Number of Subjects [planned and analyzed] section above). Baseline and other demographic characteristics were similar between the three vaccine groups. There were two PP populations: one for the analysis of the

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MenACWY objectives and another for the Tdap objectives. Since the MITT and PP population of each vaccine group did not differ by more than 4%, all immunogenicity analyses (final immunogenicity results for MenACWY and Tdap) presented in this interim CSR were carried out using the PP populations.

Of the three co-primary immunogenicity objectives, one was met and two were partially met:

The MenACWY immunogenicity analyses included two co-primary noninferiority objectives, both measured in terms of hSBA seroresponse at one month after a single injection of vaccine, administered concomitantly, sequentially, or alone:

- Noninferiority of the immune response to MenACWY when administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone, was demonstrated for all four serogroups (Table 11.4.1.1-1). The null hypothesis associated with the primary concomitant noninferiority objective for MenACWY was rejected.
- Noninferiority of the immune response to MenACWY when administered one month after Tdap, compared with the immune response to MenACWY when administered alone, was demonstrated for serogroups A, C, and Y, but not for serogroup W (Table 11.4.1.1-1). Although the sequential noninferiority criterion was not met for serogroup W, among subjects lacking bactericidal antibodies at baseline (baseline hSBA titer < 1:4), the percentage of seroresponders in the sequential administration group was high (90%). In addition, one month after MenACWY, 95% of subjects receiving MenACWY one month after Tdap had an hSBA titer ≥ 1:8 for serogroup W versus 99% of subjects receiving MenACWY one month before Tdap (Table 14.2.1.6).The null hypothesis associated with the primary sequential noninferiority objective for MenACWY was not rejected.

The Tdap immunogenicity analyses comprised one co-primary noninferiority objective, measured at one month after a single injection of vaccine, administered concomitantly or alone, in terms of: (a) percentage of subjects with antidiphtheria and antitetanus toxin

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≥1.0 IU/mL; and (b) anti-PT, anti-FHA, and anti-PRN GMCs.

- Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and Tdap, compared with the immune response to Tdap when administered alone, was demonstrated for diphtheria, tetanus, and the PT pertussis antigen, but not for FHA and PRN (Table 11.4.1.1-3). Although the concomitant noninferiority criterion was not met for FHA and PRN, the antipertussis GMCs were robust for all pertussis antigens both when Tdap was administered concomitantly and when it was administered alone (PT: 51 and 63, respectively; FHA: 341 and 511, respectively; PRN: 824 and 1198, respectively). The null hypothesis associated with the primary concomitant noninferiority objective for Tdap was not rejected.

All secondary MenACWY and Tdap noninferiority immunogenicity objectives were met:

- Noninferiority of the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥1:4, when given: (a) concomitantly with Tdap and HPV; and (b) when given one month after Tdap, was demonstrated for all four serogroups using all selected endpoints (Table 11.4.1.2-1, Table 11.4.1.2-2).The null hypotheses associated with all secondary concomitant and sequential noninferiority objectives for MenACWY were rejected.

Noninferiority of the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, and anti-PRN GMCs, when administered one month after MenACWY was demonstrated for all antigens using all selected endpoints (Table 11.4.1.2-3). The null hypotheses associated with all secondary sequential noninferiority objectives for Tdap were rejected.

Safety results

A total of 1620 subjects were enrolled in the study; all subjects were vaccinated and provided some safety data, and were therefore included in the safety population.

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Tdap was generally more reactogenic then MenACWY (69% of subjects reported solicited reactions to MenACWY versus 82% to Tdap, both administered alone). The higher reporting rates of any solicited reaction following concomitant vaccination of MenACWY, Tdap, and HPV when compared with MenACWY alone was most likely driven by the higher reactogenicity of Tdap; percentages reporting solicited reactions following Tdap administered alone and concomitantly were more balanced. There was no evidence of a negative impact on the reactogenicity profile of either MenACWY or Tdap when given sequentially. Higher percentages of subjects reported solicited local reactions to MenACWY (69%) and Tdap (82%) when administered alone than when respectively administered 1 month after Tdap (64%) and MenACWY (70%).

The most frequently reported local reaction to all vaccines was pain (range, 45% [MenACWY alone] to 71% [Tdap alone]) with no apparent difference among subjects administered MenACWY alone, sequentially, or concomitantly. Although lower percentages reported erythema and induration (range across the two reactions and vaccine groups, 12% [MenACWY alone] to 20% [Tdap alone]) than pain, reactogenicity trends were similar to those described for pain. Most solicited local reactions were experienced during the 3 days immediately following vaccination. Local reactions $\geq$ 100 mm were rare in all groups (erythema or induration $\geq$ 100 mm were reported in four MenACWY recipients and in two Tdap recipients).

Across the vaccine groups, the most commonly reported solicited systemic reactions were headache (36% to 40% after vaccination 1; 25% and 27% after vaccination 2), myalgia (19% to 27% after vaccination 1; 16% after vaccination 2), and malaise (20% to 24% after vaccination 1; 17% and 18% after vaccination 2), most of which were reported in the 3 days immediately following vaccination. Generally higher percentages reported each systemic reaction to Tdap alone than ACWY alone with highest rates observed after Tdap, MenACWY, and HPV concomitant administration. The percentages of subjects reporting any severe systemic reaction were slightly higher after concomitant administration (9%) than after administration of each of MenACWY and Tdap alone (7% for each), which was accounted for mainly by severe headache (6% in the concomitant group versus 4% following MenACWY or Tdap alone) and to a lesser

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extent by severe malaise and myalgia. Each of the other severe systemic reactions was reported by similar percentages regardless of whether ACWY or Tdap were administered alone or sequentially.

Overall, unsolicited AEs were infrequent (<20% of subjects in any vaccine group), and did not show any relevant differences between the vaccine groups or when compared across the first and second vaccinations. Overall, the percentage of subjects experiencing any unsolicited AE was similar among the three vaccine groups (range, 16% to 18%). The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was “infections and infestations” (up to 7% of the subjects in each of the three vaccine groups) which reflected common illness expected in this populations or known reactions to vaccination. In total, 71 subjects reported possibly or probably related unsolicited AEs (range, 3% to 6% per vaccine group). No SOC had more than 2% of subjects with reported AEs judged as possibly or probably related to the study vaccines and all were caused by solicited AEs continuing past the 7-day observation window or other known side effects of vaccination. Severe possibly or probably related unsolicited AEs were reported by seven subjects, three of these seven were cases of headache.

There were no deaths in this study. SAEs were reported by one subject in the concomitant vaccination group and two subjects in the MenACWY → Tdap group. None of the SAEs was assessed as related to the study vaccines. One subject ((b) (6)) withdrew due to two SAEs (Cushing's Syndrome and Pituitary Tumour Benign). No other significant AEs were reported in this study.

Conclusions

The two co-primary MenACWY immunogenicity objectives demonstrated that MenACWY can be administered either concomitantly with Tdap and HPV or sequentially, one month after Tdap, without a clinically meaningful impact on the immune response relative to MenACWY administered alone. This finding was also supported by the results observed for the secondary MenACWY endpoints.

The co-primary Tdap immunogenicity objective showed that the immunogenicity of

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Tdap administered concomitantly with MenACWY and HPV is noninferior to that of Tdap administered alone for diphtheria, tetanus and for the PT pertussis antigen. Although noninferiority was not demonstrated for the FHA and PRN pertussis antigens, the immune response, as measured by the GMCs against all three pertussis antigens, was robust both when Tdap was administered concomitantly and alone.

The safety profile of MenACWY was comparable when MenACWY was administered alone, concomitantly with Tdap and HPV, or one month after Tdap. Similarly, the safety profile of Tdap was comparable when Tdap was administered alone and concomitantly with MenACWY and HPV. Overall, reactogenicity after Tdap was higher than after MenACWY. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

Table 2-1 Time and Events

MenACWY + Tdap + HPV Group								
Study Month	**Month 0**		**Month 1**	**Month 2**		**Month 6**		**Month 7**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 181 (-28/+28)	Day 183 (+2) ☎	Day 211 (-4/+7)
Visit Number	**1**		**2**	**3**		**5**		**6**
Obtain Informed Assent and Consent	X							
Medical History	X							
Physical Assessment	X			X		X		
Pregnancy Test[b]	X			X		X		X
Obtain Blood Sample	20 mL		20 mL					20 mL
Administer Study Vaccine(s)	ACWY, Tdap, HPV			HPV		HPV		
Injection-site Examination	X			X		X		
Distribute/record Diary Card	X		X	X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X			X		X		
Collect/record Concomitant Medications*	X		X	X		X		X
Collect/record Adverse Events*	X		X	X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X
Study Termination								X

[a] Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. day 1 is defined as the first study vaccination.

[b] Urine pregnancy test will be performed on all females prior to each vaccination and 30 days after their last vaccination.

[c] Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 9.5.1-2 for further details.

☎ Telephone follow-up

Subjects in the MenACWY + Tdap + HPV group will not attend visits 4, 7 and 8.

MenACWY → Tdap Group

Study Month	Month 0		Month 1		Month 2		Month 4		Month 8		Month 9
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	ACWY		Tdap		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

[a] Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study vaccination.

[b] Urine pregnancy test will be performed on all females prior to each vaccination and 30 days after their last vaccination.

[c] Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 9.5.1-2 for further details.

☎ Telephone follow-up

Subjects in the MenACWY → Tdap group will not attend visits 5 and 6.

Tdap → MenACWY Group						
Study Month	**Month 0**	**Month 1**	**Month 2**	**Month 4**	**Month 8**	**Month 9**

Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	Tdap		ACWY		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

[a] Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study vaccination.

[b] Urine pregnancy test will be performed on all females prior to each vaccination and 30 days after their last vaccination.

[c] Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 9.5.1-2 for further details.

☎ Telephone follow-up

Subjects in the Tdap → MenACWY group will not attend visits 5 and 6.

Table 2-2 Primary Immunogenicity Objective: Percentage of Subjects (95% CI) with hSBA Seroresponse

	Variable		MenACWY + Tdap + HPV (I)	MenACWY → Tdap[a] (II)	Tdap → MenACWY (III)	Vaccine Group Differences (95% CI)	
						Concomitant (I - II)	Sequential (III - II)
A	Baseline titer	<1:4	N=460 80% (76, 84)	N=456 81% (77, 85)	N=415 87% (84, 90)	-1% (-6, 4)	6% (1, 11)
		≥ 1:4	N=37 84% (68, 94)	N=30 87% (69, 96)	N=43 81% (67, 92)	-3% (-20, 16)	-5% (-22, 14)
	Overall		N=497 80% (77, 84)	N=486 82% (78, 85)	N=458 87% (83, 90)	-1% (-6, 4)	5% (1, 10)
C	Baseline titer	<1:4	N=337 90% (86, 93)	N=355 88% (84, 91)	N=319 90% (86, 93)	1% (-3, 6)	2% (-3, 7)
		≥ 1:4	N=160 69% (62, 76)	N=132 74% (66, 81)	N=138 69% (60, 76)	-5% (-15, 6)	-5% (-16, 5)
	Overall		N=497 83% (80, 86)	N=487 84% (81, 88)	N=457 84% (80, 87)	-1% (-6, 3)	-1% (-6, 4)
W	Baseline titer	<1:4	N=257 96% (93, 98)	N=259 99% (97,100)	N=224 90% (86, 94)	-3% (-6, -1)	-9% (-14, -6)
		≥ 1:4	N=233 55% (48, 61)	N=215 59% (52, 65)	N=234 41% (35, 48)	-4% (-13, 6)	-17% (-26, -8)
	Overall		N=490 77% (73, 80)	N=474 81% (77, 84)	N=458 65% (61, 70)	-4% (-9, 1)	-16% (-21, -10)
Y	Baseline titer	<1:4	N=362 91% (88, 94)	N=362 91% (87, 94)	N=333 90% (87, 93)	1% (-4, 5)	0% (-5, 4)
		≥ 1:4	N=134 59% (50, 67)	N=125 58% (48, 66)	N=127 46% (38, 56)	1% (-11, 13)	-11% (-23, -1)
	Overall		N=496 83% (79, 86)	N=487 82% (79, 86)	N=460 78% (74, 82)	0% (-4, 5)	-4% (-9, 1)

Source: Table 14.2.1.1 (Groups I and II), Table 14.2.1.3 (Group III)
[a] MenACWY alone

Table 2-3 Primary Immunogenicity Objective: Effect of Concomitant and Sequential* Vaccination on Immunogenicity for Diphtheria, Tetanus, and Pertussis Antigens (Postvaccination Results)

		MenACWY+ Tdap + HPV (95% CI) (I)	MenACWY → Tdap (95% CI) (II)	Tdap→ MenACWY[a] (95% CI) (III)	Vaccine Group Difference (95% CI) (I - III)	Vaccine Group Ratio (95% CI) (I/III)	Vaccine Group Difference* (95% CI) (II - III)	Vaccine Group Ratio* (95% CI) (II/III)
					Concomitant		Sequential	
		N=495	**N=459**	**N=487**				
Diphtheria	% ≥1.0 IU/mL	100% (99, 100)	100% (99, 100)	98% (96, 99)	2% (1, 4)	NA	2% (1, 4)	NA
Tetanus	% ≥1.0 IU/mL	100% (99, 100)	100% (99, 100)	100% (99, 100)	0% (-1, 1)	NA	0% (-1, 1)	NA
Pertussis antigen								
PT	GMC	**N=482** 51 (47, 55)	**N=452** 79 (73, 87)	**N=477** 63 (58, 69)	NA	0.8 (0.71, 0.9)	NA	1.25 (1.11, 1.42)
FHA	GMC	**N=492** 341 (310, 375)	**N=458** 1107 (989, 1238)	**N=485** 511 (464, 563)	NA	0.67 (0.58, 0.76)	NA	2.22 (1.91, 2.59)
PRN	GMC	**N=495** 824 (732, 928)	**N=459** 1563 (1390, 1758)	**N=487** 1198 (1063, 1351)	NA	0.69 (0.58, 0.81)	NA	1.32 (1.13, 1.55)

Source: Tables 14.2.1.13 to 17 (Groups I and III); Tables 14.2.1.20 to 24 (Group II)

[a] Tdap alone

* Secondary objective

Table 2-4 Overview of Subjects with at Least One Reactogenicity Sign, Days 1 to 7 After Each Vaccination

Type of Reaction		Number (%) of Subjects With Solicited Reaction		
		MenACWY + Tdap + HPV (I)	MenACWY → Tdap (II)	Tdap → MenACWY (III)
After MenACWY or Tdap vaccination[a]				
		N=540	**N=541**	**N=539**
	Any reaction	459 (85%)[a]	450 (83%)	468 (87%)
	Local reaction	426 (79%)[a]	403 (74%)	431 (80%)
	Systemic reaction	310 (57%)	334 (62%)	358 (66%)
	Other reaction[b]	133 (25%)	143 (26%)	147 (27%)
Vaccination 1[c]		**N=540**	**N=541**	**N=539**
	Any reaction	478 (89%)	373 (69%)	443 (82%)
	Local reaction	457 (85%)	279 (52%)	399 (74%)
	Systemic reaction	310 (57%)	274 (51%)	309 (57%)
	Other reaction[b]	133 (25%)	97 (18%)	112 (21%)
Vaccination 2[d]			**N=510**	**N=503**
	Any reaction	NA	358 (70%)	322 (64%)
	Local reaction	NA	320 (63%)	260 (52%)
	Systemic reaction	NA	218 (43%)	215 (43%)
	Other reaction[b]	NA	74 (15%)	67 (13%)

Source: Table 14.3.1.1.2.1, Table 14.3.1.1.2.2, Table 14.3.1.1.2.3

[a] Group I: local reactions at MenACWY or Tdap injection sites after visit 1 vaccination; Group II: local reactions at MenACWY injection site after visit 1 vaccination, or at Tdap injection site after visit 2 vaccination; Group III: local reactions at Tdap injection site after visit 1 vaccination or at MenACWY injection site after visit 2 vaccination.

[b] analgesic/antypiretic medications used and stayed at home.

[c] Group I: reactions to MenACWY, Tdap, or HPV after visit 1 vaccination; Group II: reactions to MenACWY alone after visit 1 vaccination; Group III: reactions to Tdap alone after visit 1 vaccination.

[d] Group II: reactions to Tdap administered alone at visit 2, one month after MenACWY; Group III: reactions to MenACWY administered alone at visit 2, one month after Tdap.

Table 2-5 Overview of Unsolicited AEs

Type of Reaction	Number (%) of Subjects With Unsolicited Adverse Event		
	MenACWY + Tdap + HPV (I)	MenACWY → Tdap (II)	Tdap → MenACWY (III)
Overall	**N=540**	**N=541**	**N=539**
Any AE	92 (17%)	86 (16%)	95 (18%)
Possibly probably related AEs	24 (4%)	17% (3%)	30 (6%)
SAEs	1 (<1%)	2 (<1%)	0
AEs leading to discontinuation	1 (<1%)	0	0
Possibly probably related SAEs	0	0	0
Death	0	0	0
Onset During 1 Month After MenACWY Vaccination[a]			
	N=540	**N=541**	**N=503**
Any AE	71 (13%)	50 (9%)	40 (8%)
Possibly probably related AEs	23 (4%)	11 (2%)	13 (3%)
SAEs	1 (<1%)	0	0
AEs leading to discontinuation	1 (<1%)	0	0
Possibly probably related SAEs	0	0	0
Onset During 1 Month After Visit 1	**N=540**	**N=541**	**N=539**
Any AE	71 (13%)	50 (9%)	65 (12%)
Possibly probably related AEs	23 (4%)	11 (2%)	20 (4%)
SAEs	1 (<1%)	0	0
AEs leading to discontinuation	0	0	0
Possibly probably related SAEs	0	0	0
Onset During 1 Month After Visit 2		**N=510**	**N=503**
Any AE	NA	48 (9%)	40 (8%)
Possibly probably related AEs	NA	7 (1%)	13 (3%)
SAEs	NA	1 (<1%)	0
AEs leading to discontinuation	NA	0	0
Possibly probably related SAEs	NA	0	0

Source: Table 14.3.1.1.6, Table 14.3.1.1.7, Table 14.3.1.1.8, Table 14.3.1.1.11, Table 14.3.1.1.11.1, Table 14.3.1.1.11.2, Table 14.3.1.1.11.3, Table 14.3.1.1.14, Table 14.3.1.1.14.1, Table 14.3.1.1.14.2, Table 14.3.1.1.14.3, Table 14.3.2.2, Table 14.3.2.3

[a] Group I: summary of AEs with onset during 1 month after MenACWY+Tdap+HPV vaccination at visit 1; Group II: summary of AEs with onset during 1 month after MenACWY vaccination at visit 1; Group III: summary of AEs with onset during 1 month after MenACWY vaccination at visit 2.

2.0 SYNOPSIS

Name of Sponsor Novartis Vaccines & Diagnostics S.r.l. Via Fiorentina, 1 53100 Siena, Italy	Individual Study Table Referring to Part [ ] of the Dossier VOLUME: PAGE:	*For National Authority Use Only*
Name of Finished Product Novartis Meningococcal ACWY Conjugate Vaccine		
Name of Active Ingredient MenA, MenC, MenW, and MenY, each conjugated to CRM_{197}		

Title of Study:
A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil) in Healthy Adolescents

Protocol Number: V59P18

Investigators: Adriano Arguedas, MD

Study Centers: Instituto de Atencion Pediatrica, San Jose, Costa Rica

Publication (reference): None

Study Period: First subject enrolled: 19 JUL 2007 Last subject last visit: 30 SEP 2008	**Phase of Development:** Phase 3

Objectives:

Immunogenicity Objectives

Primary

- Demonstrate that the immune response to MenACWY, as measured by the percentage of hSBA seroresponders, when given concomitantly with Tdap and HPV is not inferior to the immune response when MenACWY is administered alone. Seroresponse: for a subject with baseline hSBA titer <1:4, seroresponse was defined as a postvaccination hSBA titer ≥ 1:8; for a subject with baseline hSBA titer ≥ 1:4, seroresponse was defined as a postvaccination hSBA titer of at least 4 times the baseline.
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-

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FHA, and anti-PRN GMCs, when given concomitantly with MenACWY and HPV, is not inferior to the immune response when Tdap is administered alone.

- Demonstrate that the immune response to MenACWY, as measured by the percentage of hSBA seroresponders, when given one month after Tdap, is not inferior to the immune response when MenACWY is administered alone, i.e. one month prior to Tdap.

Secondary

- Demonstrate that the immune response of the HPV vaccine given concomitantly with MenACWY and Tdap is not inferior to the response when HPV is given alone. Immune response against HPV virus-like particles (VLPs) for types 6, 11, 16, and 18 was measured at one month after the third HPV injection by competitive Luminex immunoassay (cLIA) in terms of: (a) anti-HPV seroconversion (SC); and (b) anti-HPV geometric mean titers (GMTs). SC was defined as negative (baseline HPV titer < type-specific cut-off) for anti-HPV and anti-HPV ≥ an HPV type-specific cut-off at one month after the third HPV injection.
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, anti-PRN GMCs, when administered one month after MenACWY is not inferior to the immune response to Tdap administered alone.
- Assess the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥1:4, when given: (a) concomitantly with Tdap and HPV; (b) alone; and (c) when given one month after Tdap.
- Assess the antidiphtheria and antitetanus GMCs and the percentage of subjects with a 4-fold rise in antibody titer over baseline against PT, FHA, PRN.

Safety Objectives

- Assess the safety profile following a single injection of MenACWY given alone one month after Tdap, compared with the safety profile following a single injection of MenACWY given alone one month before Tdap.

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- Assess the safety profile following a single injection of MenACWY given alone or concomitantly with Tdap and HPV vaccine.
- Assess the safety profile following a single injection of HPV given alone or concomitantly with Tdap and MenACWY.

Methodology:
Subjects were randomized at a 1:1:1 ratio to receive:

- MenACWY concomitantly with Tdap and HPV at study month 0 followed by two injections of HPV at month 2 and 6 (MenACWY+Tdap+HPV group);
- MenACWY at study month 0 followed by one injection of Tdap at month 1, followed by three injections of HPV at months 2, 4, and 8 (MenACWY→Tdap→HPV group);
- Tdap at month 0 followed by one injection of MenACWY at month 1, followed by three injections of HPV at months 2, 4, and 8 (Tdap→MenACWY→HPV group).

Randomization was stratified by gender and age group (11 to 14 years of age and 15 to 18 years of age). Study vaccines were administered and blood samples were obtained as summarized in the table below:

	MenACWY + Tdap + HPV	**MenACWY → Tdap → HPV[a]**	**Tdap → MenACWY → HPV[b]**
Month 0 (day 1, visit 1)	Serology [M, T, H] MenACWY+Tdap+HPV	Serology [M, H] MenACWY	Serology [T, H] Tdap
Month 1 (day 31, visit 2)	Serology [M, T]	Serology [M, T,] Tdap	Serology [M, T] MenACWY
Month 2 (day 61, visit 3)	HPV	Serology [T,] HPV	Serology [M] HPV
Month 4 (day 121, visit 4)	--	HPV	HPV
Month 6 (day 181, visit 5)	HPV	--	--
Month 7 (day 211, visit 6)	Serology [H]	--	--
Month 8 (day 241, visit 7)	--	HPV	HPV
Month 9 (day 271, visit 8)	--	Serology [H]	Serology [H]

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[M] analyzed for MenACWY; [T] analyzed for Tdap; [H] analyzed for HPV; [a] MenACWY alone; [b] Tdap alone

Number of Subjects (planned and analyzed):

A total of 1620 subjects were planned to be enrolled in the study, 540 in each of the three vaccine groups. A total of 1620 subjects were actually enrolled and vaccinated, as summarized in the table below:

Planned and Actual Enrollment and Analyses

Enrolled and vaccinated (planned)		**MenACWY + Tdap + HPV** **540** **(540)**	**MenACWY → Tdap → HPV** **541** **(540)**	**Tdap → MenACWY→ HPV** **539** **(540)**
ACWY	MITT	507 (94%)	508 (94%)	481 (89%)
	PP	496 (92%)	490 (91%)	461 (86%)
Tdap	MITT	503 (93%)	484 (89%)	498 (92%)
	PP	492 (91%)	458 (85%)	487 (90%)
HPV	MITT	475 (88%)	471 (87%)	457 (85%)
	PP	364 (67%)	381 (70%)	365 (68%)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Male or female individuals 11 to 18 years of age who gave their written assent and, if applicable, whose parents or legal guardians gave written informed consent at the time of enrollment, were virgins (both male and female) with no intention of becoming sexually active during the study period, were available for all visits and telephone calls scheduled for the study, were in good health as determined by medical history, physical assessment, and clinical judgment of the investigator, and who were properly vaccinated against diphtheria, tetanus, pertussis (i.e., who had received five doses of pediatric DTP/DTaP before their seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose was not needed).

Exclusion Criteria: Individuals not eligible to be enrolled in the study were those who:

1. were unwilling to give their written assent / consent ;
2. and/or whose parents or legal guardians were perceived to be unreliable or unavailable

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for the duration of the study period;
3. had a positive pregnancy test;
4. had a previous confirmed or suspected disease caused by *N. meningitidis*;
5. had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
6. had previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational). (exception: receipt of OMP-containing Hib vaccines was permitted);
7. had received prior human papillomavirus (HPV) vaccine;
8. had received investigational agents or vaccines within 90 days prior to enrollment or who were expected to receive an investigational agent or vaccine prior to completion of the study;
9. had received licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine was anticipated during the study period (exception: inactivated influenza vaccine may be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination);
10. who had received a live viral vaccine within 21 days prior to enrollment;
11. had experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy), or had experienced fever (defined as body temperature ≥ 38°C) within 3 days prior to enrollment;
12. had any serious acute, chronic or progressive disease such as: history of cancer, complicated diabetes mellitus, advanced arteriosclerotic disease, autoimmune disease, HIV infection or AIDS, blood dyscrasias, congestive heart failure, renal failure, severe malnutrition. *Note: Subjects with mild asthma were eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids were not eligible for enrollment.*
13. had epilepsy, any progressive neurological disease or history of Guillain-Barre syndrome;
14. had a history of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;

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15. had a condition that was a contraindication to vaccination as indicated in the most recent package inserts (including latex allergy);
16. had a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example): receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose of more than 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy); (ii) receipt of immunostimulants; (iii) receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study.
17. were known to have a bleeding diathesis or any condition that could be associated with a prolonged bleeding time;
18. had Down's syndrome or other known cytogenic disorders;
19. and/or whose families were planning to leave the area of the study site before the end of the study period;

had any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Test Product, Dose, Mode of Administration, Lot Number:
MenACWY conjugate vaccine, lot Z79P40I1, expiry date: Feb 2008. A 0.5 mL injectable solution, administered by intramuscular injection (IM) in the right deltoid area, contained 10µg MenA and 5µg of each of MenC, MenW, and Men Y, each conjugated to CRM_{197}.

MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM197-MenC conjugate	5 µg MenC, (b) (4) µg CRM197
CRM197-MenW conjugate	5 µg MenW, (b) (4) µg CRM197
CRM197-MenY conjugate	5 µg MenY, (b) (4) µg CRM197
Sodium chloride	(b) (4)
Sucrose	
Sodium phosphate buffer	
Potassium dihydrogen phosphate	
WFI	qs to 0.5 mL

Duration of Study: The actual duration of the study was approximately 15 months (19 July 2007 to 30 September 08), including approximately five months of enrolment (19 July 2007 to 11 December 2007) and nine months of individual study participation.

Reference Therapy, Dose, Mode of Administration, Lot Number:
1) HPV vaccine (Merck & Co. Gardasil), lot 0515U, expiry date: 10 Feb 2010. A 0.5 mL injectable solution was administered IM in the upper anterolateral area of the thigh.

HPV Vaccine (Gardasil) Composition

Composition	Quantity per 0.5 mL dose
HPV 6 L1 protein	20 mcg
HPV 11 L1 protein	40 mcg
HPV 16 L1 protein	40 mcg
HPV 18 L1 protein	20 mcg

Other ingredients included amorphous aluminum hydroxyphosphate sulphate adjuvant (225 micrograms aluminum), sodium chloride, L-histidine, Polysorbate 80, sodium borate, and

2) Tdap vaccine (GSK US-licensed Boostrix, available commercial lots). A 0.5 mL injectable solution was administered IM in the left deltoid area.

Tdap Vaccine (US-licensed Boostrix) Composition

Composition	Quantity per 0.5 mL dose
Tetanus toxoid (T)	5 Lf
Diphtheria toxoid (d)	2.5 Lf
Inactivated PT	8 µg
Filamentous hemagglutinin (FHA)	8 µg
Pertactin (PRN)	2.5 µg

Other ingredients included NaCl (4.5 mg), aluminum adjuvant (not more than 0.39 mg aluminum by assay), ≤100 mcg of residual formaldehyde, and ≤ 100 mcg of polysorbate 80 (Tween 80).

Criteria for Evaluation:

Immunogenicity

Primary:

- Concomitant noninferiority for MenACWY: lower limit of the two-sided 95% confidence interval (CI) of the difference in the percentages of seroresponders for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone) to be > -10%;
- Concomitant noninferiority for Tdap:
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY+HPV+Tdap minus Tdap alone) to be > -10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, anti-PRN GMCs (MenACWY+HPV+Tdap / Tdap alone) to be > 0.67.
- Sequential noninferiority for MenACWY: lower limit of the two-sided 95% CI of the difference in the percentages of seroresponders for each serogroup (Tdap → MenACWY→HPV minus MenACWY alone) to be > -10%.

Secondary:

- Concomitant noninferiority for HPV
  - lower limit of the two-sided 95% CI of the difference in the percentages for anti-HPV seroconversion for each HPV type as measured by cLIA (MenACWY+Tdap+HPV minus HPV alone) to be > -5%.
  - lower limit of the two-sided 95% CI of the anti-HPV GMT ratio (MenACWY+Tdap+HPV / HPV alone) to be > 0.5 for each HPV type.
- Sequential noninferiority for Tdap
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY → Tdap →HPV minus Tdap alone) to be >-10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, and anti-PRN GMCs (MenACWY → Tdap →HPV / Tdap alone) to be >0.67.
- Concomitant and sequential noninferiority for MenACWY (criteria non pre-specified in the study protocol):
  - lower limit of the two-sided 95% CI of the difference in the percentages for hSBA ≥ 1:8 and ≥ 1:4 for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone; Tdap → MenACWY→HPV minus MenACWY alone) to be >-10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratio of the hSBA GMTs (MenACWY+HPV+Tdap / MenACWY alone; Tdap → MenACWY→HPV / MenACWY alone) to be >0.5.

The antidiphtheria and antitetanus GMCs and the percentage of subjects with at least a 4-fold rise in antibody titer over baseline against PT, FHA, and PRN, secondary endpoints for

the assessment of both concomitant and sequential administration of Tdap, were evaluated descriptively

Safety

The measures of safety used in this study consisted of solicited local and systemic reactions and other unsolicited adverse events.

Statistical Methods:

Noninferiority Immunogenicty Analysis

For MenACWY seroresponse, for serogroups A, C, W and Y, the two-sided 95% CIs for the vaccine group differences (MenACWY+Tdap+HPV minus MenACWY alone; Tdap → MenACWY →HPV minus MenACWY alone) in the percentage of subjects with hSBA seroresponse were computed at one month after vaccination with MenACWY.

For hSBA GMTs, for serogroups A, C, W and Y, the two-sided 95% CIs of the GMTs ratios between the vaccine groups (MenACWY+Tdap+HPV / MenACWY alone; Tdap → MenACWY →HPV / MenACWY alone) were computed using an ANOVA model with vaccination group, gender, and age group as factors.

For anti-D and anti-T antibodies, the two-sided 95% CIs for the vaccine group differences (MenACWY+Tdap+HPV minus Tdap alone; MenACWY → Tdap →HPV minus Tdap alone) in the percentage of subjects with ELISA antibody concentrations ≥ 1.0 IU/mL, were calculated for each antigen at one month after vaccination with Tdap.

For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between the vaccine groups (MenACWY+Tdap+HPV / Tdap alone; MenACWY → Tdap → HPV / Tdap alone) were computed using an ANCOVA model with vaccine group, gender, and age group as fixed effects and the log10 transformed prevaccination ELISA concentrations as covariate.

For anti-HPV-6, anti-HPV-11, anti-HPV-16, and anti-HPV-18 seroconversion response, two-sided 95% CIs for the vaccine group differences (MenACWY+Tdap+HPV minus HPV alone) in the percentage of subjects with anti-HPV seroconversion were computed for each HPV type at one month after the third HPV vaccination.

For anti-HPV-6, anti-HPV-11, anti-HPV-16, and anti-HPV-18 GMTs, two-sided 95% CI of the GMT ratio between the vaccine groups (MenACWY+Tdap+HPV / HPV alone) were computed for each HPV type, at one month after the third HPV vaccination, using an ANOVA model with vaccination group, gender, and age group as factors.

All noninferiority criteria are provided under “Criteria for Evaluation” in this synopsis.

Analysis of Safety

The analyses of safety were performed on all subjects who received at least one injection and provided postbaseline safety data.

The percentage of subjects with solicited local (pain, erythema and induration) and systemic reactions (chills, nausea, malaise, myalgia, arthralgia, headache, fever and rash) during the 7 days (day 1 to 7) follow-up period after each vaccination were tabulated. For each solicited local and systemic reaction, differences between the vaccine groups were analyzed using Pearson’s chi-square test or Fisher’s Exact test where appropriate, due to small expected cell

sizes. For all vaccine groups, the percentage of subjects with at least one unsolicited adverse event (AE) up to one month after each vaccination was tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. All reported AEs, as well as AEs at least possibly related to study vaccines, were tabulated according to system organ classes (SOC) and preferred terms within each SOC.

Summary and Conclusions:

Immunogenicity results

A total of 1620 subjects were enrolled and randomized at a 1:1:1 ratio to one of the three vaccine groups. Baseline and other demographic characteristics of the enrolled population were similar between the three vaccine groups. There were three PP populations: one for the analysis of the MenACWY objectives, one for the Tdap objectives, and one for the HPV objectives. Since the MenACWY and Tdap MITT and PP population of each vaccine group did not differ by more than 4%, all immunogenicity analyses were carried out using the PP populations. The MITT and PP populations for the analysis of the HPV objectives differed by 17% to 21%; therefore, all HPV immunogenicity analyses were performed both for the MITT and PP populations. The main immunogenicity analyses were performed on the PP population.

Of the three co-primary immunogenicity objectives, one was met and two were partially met:

The MenACWY immunogenicity analyses included two co-primary noninferiority objectives, both measured in terms of hSBA seroresponse at one month after a single injection of vaccine, administered concomitantly, sequentially, or alone:

- Noninferiority of the immune response to MenACWY when administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone, was demonstrated for all four serogroups. The null hypothesis associated with the primary concomitant noninferiority objective for MenACWY was rejected.

- Noninferiority of the immune response to MenACWY when administered one month after Tdap, compared with the immune response to MenACWY when administered alone, was demonstrated for serogroups A, C, and Y, but not for serogroup W. Although the sequential noninferiority criterion was not met for serogroup W, among subjects lacking bactericidal antibodies at baseline (baseline hSBA titer < 1:4), the percentage of seroresponders in the sequential administration group was high (90%). In addition, one month after MenACWY, 95% of subjects receiving MenACWY one month after Tdap had an hSBA titer ≥ 1:8 for serogroup W versus 99% of subjects receiving MenACWY one month before Tdap.The null hypothesis associated with the primary sequential noninferiority objective for MenACWY was not rejected.

The Tdap immunogenicity analyses comprised one co-primary noninferiority objective,

measured at one month after a single injection of vaccine, administered concomitantly or alone, in terms of: (a) percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL; and (b) anti-PT, anti-FHA, and anti-PRN GMCs.

- Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, was demonstrated for diphtheria, tetanus, and the PT pertussis antigen, but not for FHA and PRN. Although the concomitant noninferiority criterion was not met for FHA and PRN, the antipertussis GMCs were robust for all pertussis antigens both when Tdap was administered concomitantly and when it was administered alone (PT: 51 and 63, respectively; FHA: 342 and 511, respectively; PRN: 819 and 1197, respectively). The null hypothesis associated with the primary concomitant noninferiority objective for Tdap was not rejected.

The secondary HPV noninferiority immunogenicity objective was met:

- Noninferiority of the immune response to the HPV vaccine, as measured at one month after the third HPV injection, in terms of: (a) anti-HPV seroconversion; and (b) anti-HPV GMTs, was demonstrated for all four HPV types, both in the MITT and PP populations. The null hypotheses associated with the secondary noninferiority objective for the HPV vaccine were rejected.

All secondary MenACWY and Tdap noninferiority immunogenicity objectives were met:

- Noninferiority of the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥ 1:4, when given: (a) concomitantly with Tdap and HPV; and (b) when given one month after Tdap, was demonstrated for all four serogroups using all selected endpoints.The null hypotheses associated with all secondary concomitant and sequential noninferiority objectives for MenACWY were rejected.

Noninferiority of the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, and anti-PRN GMCs, when administered one month after MenACWY was demonstrated for all antigens using all selected endpoints. The null hypotheses associated with all secondary sequential noninferiority objectives for Tdap were rejected.

Safety results

A total of 1620 subjects were enrolled in the study; all subjects were vaccinated and provided some safety data, and were therefore included in the safety population.

Tdap was generally more reactogenic then MenACWY (69% of subjects reported solicited reactions to MenACWY vs. 82% to Tdap, both administered alone). The higher reporting rates of any solicited reaction following concomitant vaccination of MenACWY, Tdap, and HPV when compared with MenACWY alone was most likely driven by the higher

reactogenicity of Tdap; percentages reporting solicited reactions following Tdap administered alone and concomitantly were more balanced. There was no evidence of a negative impact on the reactogenicity profile of either MenACWY or Tdap when given sequentially. Higher percentages of subjects reported solicited local reactions to MenACWY (69%) and Tdap (82%) when administered alone than when respectively administered one month after Tdap (64%) and MenACWY (70%).

Higher reporting rates of any solicted reaction were observed when the first HPV vaccine was administered concomitantly with MenACWY and Tdap than when it was administered alone (77% vs. 51% to 56%). After the second and third HPV injections, administered alone in all three vaccine groups, the reporting rates were similar across the vaccine groups and slightly higher after the third than after the second HPV vaccination (range, 50% to 55% and 53% to 58% after the second and third HPV vaccinations, respectively).

The most frequently reported local reaction to MenACWY and Tdap was pain (range, 45% [MenACWY alone] to 71% [Tdap alone]) with no apparent difference among subjects administered MenACWY alone, sequentially, or concomitantly. Although lower percentages reported erythema and induration (range across the two reactions and vaccine groups, 12% [MenACWY alone] to 20% [Tdap alone]) than pain, reactogenicity trends were similar to those described for pain. Most solicited local reactions were experienced during the 3 days immediately following vaccination. Local reactions ≥ 100 mm were rare in all groups (erythema or induration ≥ 100 mm were reported in four MenACWY recipients and in two Tdap recipients).

After the first HPV injection, all of the selected local reactions were more frequently reported when the HPV vaccine was administered concomitantly with MenACWY and Tdap than when it was administered alone (pain: 49% vs. 36% to 42%; erythema: 14% vs. 7% to 9%; induration: 10% vs. 5%). After the second and third HPV vaccination, the reporting rates for all three selected local reactions were similar across the three vaccine groups and slightly higher after the third than after the second HPV vaccination. Severe pain was reported by 5% after the concomitant administration of HPV with MenACWY and Tdap and by 2% to 4% when HPV was administered alone. Severe erythema and severe induration were rare across all HPV vaccinations and groups – severe erythema was reported by only one subject, and severe induration by three.

Across the vaccine groups, the most commonly reported solicited systemic reactions after receiving MenACWY or Tdap were headache (36% to 40% after vaccination at visit 1; 25% and 27% after vaccination at visit 2), myalgia (19% to 27% after vaccination at visit 1; 16% after vaccination at visit 2), and malaise (20% to 25% after vaccination at visit 1; 18% after vaccination at visit 2), most of which were reported in the 3 days immediately following vaccination. Generally higher percentages reported each systemic reaction to Tdap alone than MenACWY alone with highest rates observed after Tdap, MenACWY, and HPV concomitant administration. The percentages of subjects reporting any severe systemic reaction were slightly higher after concomitant administration (9%) than after administration

of MenACWY or Tdap alone at visit 1 (7% for each), which was accounted for mainly by severe headache (6% in the concomitant group versus 4% following MenACWY or Tdap alone) and to a lesser extent by severe malaise and myalgia. Each of the other severe systemic reactions was reported by similar percentages regardless of whether ACWY or Tdap were administered alone or sequentially.

After the first HPV vaccination, the reporting rates for all selected systemic reactions were higher when the HPV vaccine was administerd concomitantly with MenACWY and Tdap than when it was administered alone. After the second and third HPV vaccinations, the reporting rates were similar across the three vaccine groups and HPV vaccinations. The most frequently reported systemic reaction was headache (after the first HPV vaccination: 40% [concomitant] and 19% to 20% [alone]; after the second and third HPV vaccinations, range 15% to 18%).

Overall, unsolicited AEs were reported by similar percentages across the three vaccine groups (28% to 29%). The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was “infections and infestations” (12% to 13% of the subjects across the three vaccine groups) which reflected common illness expected in this populations or known reactions to vaccination. In total, 109 subjects reported possibly or probably related unsolicited AEs (range, 6% to 8% per vaccine group). No SOC had more than 4% of subjects with reported AEs judged as possibly or probably related to the study vaccines and most were identified thorugh the collection of solicited reactions continuing past the 7-day observation window or were other known side effects of vaccination. Severe possibly or probably related unsolicited AEs were reported by nine subjects, six of these nine were cases of headache.

There were no deaths in this study. Twelve SAEs were reported by eleven subjects. None of the SAEs was assessed as related to the study vaccines. One subject (b) (6)) withdrew due to two SAEs (Cushing's Syndrome and Pituitary Tumour Benign). No other significant AEs were reported in this study.

Conclusions

The results of the analysis of the two co-primary MenACWY immunogenicity objectives demonstrated that MenACWY can be administered either concomitantly with Tdap and HPV or sequentially, one month after Tdap, without a clinically meaningful impact on the immune response relative to MenACWY administered alone. This finding was also supported by the results observed for the secondary MenACWY endpoints.

The results of the analysis of the co-primary Tdap immunogenicity objective showed that the immunogenicity of Tdap administered concomitantly with MenACWY and HPV is noninferior to that of Tdap administered alone for diphtheria, tetanus and for the PT pertussis antigen. Although noninferiority was not demonstrated for the FHA and PRN pertussis antigens, the immune response, as measured by the GMCs against all three pertussis antigens, was robust both when Tdap was administered concomitantly and alone.

Using both protocol-specificied secondary endpoints, immunogenicity of the HPV vaccine administered concomitantly with MenACWY and Tdap was shown to be noninferior to the immunogenicity of the HPV vaccine administered alone for all four HPV types.

The safety profile of MenACWY was comparable when MenACWY was administered alone, concomitantly with Tdap and HPV, or one month after Tdap. Similarly, the safety profile of Tdap was comparable when Tdap was administered alone and concomitantly with MenACWY and HPV. Overall, reactogenicity after Tdap was higher than after MenACWY. In neither instance was the reactogenicity of one diphtheria-containing vaccine (Tdap or MenACWY) enhanced when administered after the other. The first HPV injection was more reactogenic when administered concomitantly with MenACWY and Tdap than when it was administered alone. The reactogenicity profiles after the second and third HPV injections, administered alone in all three vaccine groups, were similar across the vaccine groups. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

Table 2-1 Time and Events

MenACWY + Tdap + HPV Group								
Study Month	**Month 0**		**Month 1**	**Month 2**		**Month 6**		**Month 7**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 181 (-28/+28)	Day 183 (+2) ☎	Day 211 (-4/+7)
Visit Number	**1**		**2**	**3**		**5**		**6**
Obtain Informed Assent and Consent	X							
Medical History	X							
Physical Assessment	X			X		X		
Pregnancy Test[b]	X			X		X		X
Obtain Blood Sample	20 mL		20 mL					20 mL
Administer Study Vaccine(s)	ACWY Tdap, HPV			HPV		HPV		
Injection-site Examination	X			X		X		
Distribute/record Diary Card	X		X	X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events[d]	X			X		X		
Collect/record Concomitant Medications[d]	X		X	X		X		X
Collect/record Adverse Events[d]	X		X	X		X		X
Collect/record SAEs and AEs leading to early study withdrawal[cd]	X	X	X	X	X	X	X	X
Study Termination								X

[a]Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 was defined as the first study vaccination.
[b]Urine pregnancy test was performed on all females prior to each vaccination and 30 days after their last vaccination.
[c]Any subject who terminated early had a follow–up safety phone call six months after their last MenACWY injection.
[d]Refer to Table 9.5.1-2 for further details.
☎ Telephone follow-up
Subjects in the MenACWY + Tdap + HPV group did not attend visits 4, 7 and 8.

MenACWY → Tdap → HPV Group											
Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	ACWY		Tdap		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events[d]	X		X		X		X		X		
Collect/record Concomitant Medications[d]	X		X		X		X		X		X
Collect/record Adverse Events[d]	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal[cd]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

[a]Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 was defined as the first study vaccination.
[b]Urine pregnancy test was performed on all females prior to each vaccination and 30 days after their last vaccination.
[c]Any subject who terminated early had a follow–up safety phone call 6 months after their last MenACWY injection.
[d]Refer to Table 9.5.1-2 for further details.
☎ Telephone follow-up
Subjects in the MenACWY → Tdap → HPV group did not attend visits 5 and 6.

Tdap → MenACWY → HPV Group											
Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	Tdap		ACWY		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events[d]	X		X		X		X		X		
Collect/record Concomitant Medications[d]	X		X		X		X		X		X
Collect/record Adverse Events[d]	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal[cd]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

[a]Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed Day 1 was defined as the first study vaccination
[b]Urine pregnancy test was performed on all females prior to each vaccination and 30 days after their last vaccination
[c]Any subject who terminated early had a follow–up safety phone call 6 months after their last MenACWY injection
[d]Refer to Table 9 5 1-2 for further details
☎ Telephone follow-up
Subjects in the Tdap → MenACWY → HPV group did not attend visits 5 and 6.

NOVARTIS
VACCINES

PERIODIC ADVERSE EXPERIENCE REPORT (QUARTERLY REPORT)

For

ACTIVE SUBSTANCE(S):	**Conjugated oligosaccharides of *Neisseria meningitidis*, serogroups A, C, Y and W-135**
MEDICINAL PRODUCTS COVERED:	**Meningococcal (Serogroups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine, (Menveo®)**
US LICENSE NUMBER	**1751**
SUBMISSION TRACKING NUMBER (STN)	**125300/0**

PERIOD COVERED BY THIS REPORT

From February 19, 2010 to May 18, 2010 (data lock point)

Date of this report: June 3, 2010

REPORT NUMBER	1
MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:	Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue Cambridge, MA 02139.
NAME AND CONTACT DETAILS OF THE AUTHOR:	SABINE HAERTEL, MD, PhD Pharmacovigilance Novartis Vaccines & Diagnostics GmbH Emil-von-Behring-Str. 76 35041 Marburg, Germany Phone +49 6421 39 2679 Fax +49 6421 39 3662 Email: sabine.haertel@novartis.com
SIGNATURE:	S. Hae

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Appendix 1 Package insert

Appendix 2 Index line listing of all non-15-day alert cases

Appendix 3 VAERS Forms

1 NARRATIVE SUMMARY AND ANALYSIS

1.1 Introduction and overview

This report summarizes Menveo Adverse Event cases from the US and 15-day alert cases from foreign countries between February 19, 2010 to May 18, 2010 received by Pharmacovigilance Novartis Vaccines and Diagnostics.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

During the reporting period no initial 15-day alert reports were submitted to FDA.
There were 13 non-serious cases reported from the US (see Appendix 2 and 3)

1.2 Line listing of 15-day alert cases submitted during the reporting period

Not applicable

1.3 Summary tabulation by body system

Not applicable

1.4 Clinical significance of 15-day alert reports

Not applicable

1.5 Analysis and conclusion

It is concluded that the current safety information for Menveo is sufficient and no changes are required.

2 NARRATIVE DISCUSSION OF ACTIONS TAKEN

During the reporting period there were no actions taken due to safety reasons. No changes to the content of the package insert were required.
The currently valid package insert is provided in Appendix 1.

3 INDEX LINE LISTINGS

A listing of non-15-alert cases (all serious listed as well as non-serious listed and unlisted cases) having occurred in the United States during the reporting period is provided in Appendix 2.

4 VAERS FORMS

See Appendix 3 for the VAERS forms of all non-15-day alert cases as listed in the index line listing in Appendix 2 received during the reporting period.

NOVARTIS
VACCINES

PERIODIC ADVERSE EXPERIENCE REPORT (QUARTERLY REPORT)

For

ACTIVE SUBSTANCE(S):	**Conjugated oligosaccharides of *Neisseria meningitidis*, serogroups A, C, Y and W-135**
MEDICINAL PRODUCTS COVERED:	**Meningococcal (Serogroups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine, (Menveo®)**
US LICENSE NUMBER	**1751**
SUBMISSION TRACKING NUMBER (STN)	**125300/0**

PERIOD COVERED BY THIS REPORT

From May 19, 2010 to Aug 18, 2010 (data lock point)

Date of this report: September 3, 2010

REPORT NUMBER	2
MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:	Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue Cambridge, MA 02139.
NAME AND CONTACT DETAILS OF THE AUTHOR:	Kerstin Engelhard, MD Pharmacovigilance Novartis Vaccines & Diagnostics GmbH Emil-von-Behring-Str. 76 35041 Marburg, Germany Phone +49 6421 39 3470 Fax +49 6421 39 3662 Email: kerstin.engelhard@novartis.com
SIGNATURE:	Kerstin Engelhard

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Appendix 1 Listing of all 15-day alert cases submitted to VAERS

Appendix 2 Line listing of all terms sorted by body system

Appendix 3 Package insert

Appendix 4 Index line listing of all non-15-day alert cases

Appendix 5 VAERS Forms

1 NARRATIVE SUMMARY AND ANALYSIS

1.1 Introduction and overview

This report summarizes Menveo Adverse Event cases from the US and 15-day alert cases from foreign countries between May 19, 2010 to Aug 18, 2010 received by Pharmacovigilance Novartis Vaccines and Diagnostics.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

During the reporting period four 15-day alert reports including one follow-up report (PHHY2010US47298) were submitted to FDA.

In addition this report includes 76 VAERS forms of serious listed and non-serious (listed and unlisted) cases. Of those no cases were assessed as serious and listed, no cases were non-serious and listed, and 76 cases were non-serious and unlisted.

Of those 76 non-serious and unlisted cases there were 66 cases of 'drug administration errors'. In these cases the patients received only the diluent component of Menveo instead of the combinition of the diluent component of Menveo with the lyophilized component.

1.2 Line listing of 15-day alert cases submitted during the reporting period

Appendix 1 includes all 15-day alert cases submitted during the reporting period, identified by manufacturer number, the adverse experience terms, and the date of submission.
During the reporting period four 15-day alert reports including one follow-up report (PHHY201047298) were submitted.

1.3 Summary tabulation by body system

The summary tabulation is provided under Appendix 2. It is ordered by body system and includes all adverse experience terms and counts of occurrences received during the reporting period. As one report can include several terms, the total number of terms is higher than the total number of cases received.

1.4 Clinical significance of 15-day alert reports

In the following all 15-day alert cases are presented according to body system. A narrative description and an evaluation are provided for each case. Evaluation consists of the assessment of expectedness and causality by the company.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

PHHY2010AT37194:
Initial Austrian Health Authority report received on 09 Jun 2010: The patient was vaccinated with Menveo (meningococcal group A, C, W135 and Y conjugate vaccine, batch number 100014) 0.5 ml, intramuscularly, on an unspecified date. 10 hours after vaccination, the patient presented with increased body temperature, severe headache, reddening and swelling at the injection site (size about 7 x 4 cm) on 14 May 2010 which persisted for 3 days. Final outcome of the events was reported as complete recovery.
Company assessment:
Serious spontaneous report.
Headache, Body temperature increased [medically significant], already listed in the Core Data Sheet. All remaining reported leading events and associated symptoms were assessed as non-serious by the Novartis Medical Safety Physician.
Due to time interval to vaccination of ten hours causality could not be excluded.

EAR AND LABYRINTH DISORDERS

PHHY2010DE48116:
Combined initial health care professional report received on 20 Jul 2010 and follow up report received on 22 Jul 2010: This patient with medical history of scarlet fever within four weeks before vaccination, received Menveo (meningococcal (groups a, c, y and w-135) oligosaccharide diphtheria crm197 conjugate vaccine, batch number 030011) 0.5 ml intramuscularly into the right arm deltoid muscle on 28 Jun 2010 in the evening. The patient was concomitantly vaccinated with human diploid cell (HCD) (rabies vaccine) 1 ml intramuscularly in the left arm deltoid muscle on 28 Jun 2010 also. On 30 Jun 2010, two days after vaccination with Menveo, the patient experienced severe local reaction on the right (vaccinated) arm with discoloration and signs of inflammation and pain at injection site (right arm). On an unknown date, three days after vaccination, the patient experienced defective hearing in right ear and dizziness which persisted for one week. On an unknown date, the patient had laboratory test done whose result was normal. The outcome of the event was reported as recovered on day 9 after vaccination. The causality was not reported.
Company assessment:
Serious spontaneous report.
Hearing impaired [medically significant], assessed as unlisted according to the Core Data Sheet. The information provided in this individual case does not warrant a change to the Core Data Sheet text. The topic will be monitored closely.
The remaining reported leading events were assessed as non-serious by Novartis Medical Safety Physician.
Due to time interval to vaccination of two days causality could not be excluded. However other alternative causes (concomitant vaccination with rabies vaccine) provide a possible explanataion for the reported adverse events.

NERVOUS SYSTEM DISORDER

PHHY2010US47298:
Initial report received from a nurse on 15 Jul 2010: This patient was vaccinated with Menveo (meningococcal groups A, C, Y and W-135 oligosaccharide diphtheria CRM197 conjugate vaccine; batch number: unknown) on an unspecified date. The patient concomitantly received hepatitis A vaccine (manufacturer unknown). The patient experienced syncope associated with "seizure like movements". The patient fell and struck his head. The patient was admitted to hospital on an unknown date. The outcome of the events was not reported.
Follow up report received from a physician on 22 Jul 2010: The patient had history of mild aortic regurgitation and syncope (two times). The hepatitis A vaccine was confirmed as Havrix (non-Novartis vaccine). CAT scan was negative. The patient also experienced tonic convulsion. The patient was discharged on an unknown date. The syncope work up was in progress. Final outcome was not reported.
Follow up report received from the physician on 10 Aug 2010: The physician confirmed that ten to fifteen minutes after vaccination, the patient experienced tonic convulsions.
Follow up report received from the physician on 16 Aug 2010: The patient had no history of previous brain injury. There were no syncopal episodes after previous vaccinations. The patient was vaccinated with Menveo (lot number: 160004) on 07 Jul 2010. The patient was diagnosed with closed head trauma secondary to syncope and fever on 07 Jul 2010. Final outcome of the events was not reported.
Company assessment:
Serious spontaneous report.
Tonic convulsion, syncope [hospitalisation], assessed as unlisted according to the Core Data Sheet.
The information provided in this individual case does not warrant a change to the Core Data Sheet text. The topic will be monitored closely.
The remaining reported event was assessed as non-serious by Novartis Medical Safety Physician.
Lack of data does not allow detailed medical assessment; but time relation to vaccination of 5 min could be plausible for a causal relationship. However other alternative causes (underlying condition of mild aortic regurgitation and syncopes) provide a possible explanation for the reported adverse events.

1.5 Analysis and conclusion

No increased frequency of already known side effects has been observed. From the serious unexpected adverse experiences during the reporting period, no new safety signal has been seen.

It is concluded that the current safety information for Menveo is sufficient and no changes are required.

2 NARRATIVE DISCUSSION OF ACTIONS TAKEN

During the reporting period there were no actions taken due to safety reasons. No changes to the content of the package insert were required.
The currently valid package insert is provided in Appendix 3.

3 INDEX LINE LISTINGS

A listing of non-15-alert cases (all serious listed as well as non-serious listed and unlisted cases) having occurred in the United States during the reporting period is provided in Appendix 4.

4 VAERS FORMS

See Appendix 5 for the VAERS forms of all non-15-day alert cases received during the reporting period.

NOVARTIS
VACCINES

PERIODIC ADVERSE EXPERIENCE REPORT (QUARTERLY REPORT)

For

ACTIVE SUBSTANCE(S):	**Conjugated oligosaccharides of *Neisseria meningitidis*, serogroups A, C, Y and W-135**
MEDICINAL PRODUCTS COVERED:	**Meningococcal (Serogroups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine, (Menveo®)**
US LICENSE NUMBER	**1751**
SUBMISSION TRACKING NUMBER (STN)	**125300/0**

PERIOD COVERED BY THIS REPORT

From Aug 19, 2010 to Nov 18, 2010 (data lock point)

Date of this report: December 8, 2010

REPORT NUMBER	3
MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:	Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue Cambridge, MA 02139.
NAME AND CONTACT DETAILS OF THE AUTHOR:	Kerstin Engelhard, MD Pharmacovigilance Novartis Vaccines & Diagnostics GmbH Emil-von-Behring-Str. 76 35041 Marburg, Germany Phone +49 6421 39 3470 Fax +49 6421 39 3662 Email: kerstin.engelhard@novartis.com
SIGNATURE:	K. Engelhard

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Appendix 1 Listing of all 15-day alert cases submitted to VAERS

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Appendix 4 Index line listing of all non-15-day alert cases

Appendix 5 VAERS Forms

1 NARRATIVE SUMMARY AND ANALYSIS

1.1 Introduction and overview

This report summarizes Menveo Adverse Event cases from the US and 15-day alert cases from foreign countries between Aug 19, 2010 to Nov 18, 2010 received by Pharmacovigilance Novartis Vaccines and Diagnostics.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

During the reporting period nine 15-day alert reports including one follow-up report (PHHY2010US47298) were submitted to FDA. Case PHHY2010DE74470 was a duplicate from case PHHY2010DE67070. Case PHHY2010US59181 is still listed in the "Index line listing of all non 15-day alert cases", because the case was initially "not serious" and was assessed "serious" after receipt of the follow-up report, which was submitted in the following reporting period.

In addition this report includes 50 VAERS forms of serious listed and non-serious (listed and unlisted) cases. Of those no cases were assessed as serious and listed, four cases were non-serious and listed, and 46 cases were non-serious and unlisted.

Of those 46 non-serious and unlisted cases there were 35 cases of 'drug administration errors'. In these cases the patients received only the diluent containing the C,Y and W-135 components of Menveo instead of the combinition of the diluent component of Menveo with the lyophilized containing the A component.

1.2 Line listing of 15-day alert cases submitted during the reporting period

Appendix 1 includes all 15-day alert cases submitted during the reporting period, identified by manufacturer number, the adverse experience terms, and the date of submission.
During the reporting period nine 15-day alert reports including one follow-up report (PHHY2010US47298) were submitted.

1.3 Summary tabulation by body system

The summary tabulation is provided under Appendix 2. It is ordered by body system and includes all adverse experience terms and counts of occurrences received during the reporting period. As one report can include several terms, the total number of terms is higher than the total number of cases received.

1.4 Clinical significance of 15-day alert reports

In the following all 15-day alert cases are presented according to body system. A narrative description and an evaluation are provided for each case. Evaluation consists of the assessment of expectedness and causality by the company.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

PHHY2010AT62397:
Initial Health Authority report (ref no. 34672) received on 20 Sep 2010: This adolescent was vaccinated with Menveo (men a conjugate - crm 197, men c conjugate - crm 197, men w conjugate - crm 197, men y conjugate - crm 197, batch number not reported) 0.5 ml, intramuscularly on 17 Aug 2010. On 18 Aug 2010, the adolescent presented with fever (temperature of 38.7 degree Celsius) and on 19 Aug 2010 the adolescent experienced fatigue, arthralgia and headache. The outcome of the events was reported as completely recovered. The causality was reported as suspected and the seriousness criteria were reported as medically significant.
Company assessment:
Serious spontaneous report
Fever, Fatigue, Arthralgia, Headache [medically significant] assessed as listed in the Core Data Sheet.
Time relation to vaccination of one day is plausible for a causal relation.

INFECTIONS AND INFESTATIONS

PHHY2010US59181:
Initial report received from a nurse on 03 Sep 2010: This patient was vaccinated with Menveo ((men a conjugate - crm 197, men c conjugate - crm 197, men w conjugate - crm 197, men y conjugate - crm 197, batch number: 10003), 0.5 ml intramuscularly, on 04 Aug 2010. Following administration with vaccine, the patient developed a diffuse, red, itchy rash on the face, trunk and limbs of the body on 08 Aug 2010. The outcome of the events was not reported.
Follow up report received from a nurse on 17 Nov 2010: The patient experienced severe rash on 05 Aug 2010 which was previously reported as 08 Aug 2010. After one month, diagnosis of strep throat with scarlet fever was made. The patient was given treatment with antibiotics. The patient recovered from severe rash on 05 Sep 2010 and the outcome of the event sore throat with scarlet fever was reported as condition improving.
Serious spontaneous report
Pharyngitis streptococcal [medically significant] assessed as unlisted according to the Core Data Sheet.
The information provided in this individual case does not warrant a change to the Core Data Sheet text. The topic will be monitored closely.
Menveo is an inactivated vaccine and does not induce streptococcus infection.

NERVOUS SYSTEM DISORDER

PHHY2010DE67070:
Initial report received from a consumer (who was a (b) (6)) on 27 Sep 2010: This patient with an unknown medical history was vaccinated first time with Menveo (quadrivalent conjugated meningococcal vaccine against Neisseria meningitides serogroups A, C, W-135 and Y; batch number A10044) on 16 Sep 2010. After vaccination, the patient developed facial paresis (no side reported), ptosis, dizziness (recurrent), headache, and otalgia on 23 Sep 2010. No hospitalization took place. Outcome of the events was reported as condition unchanged.
Follow up report received from consumer on 20 Oct 2010: The patient had a medical history of allergy to house dust mite and pollen. The patient was vaccinated with Menveo in the right deltoid muscle, intramuscularly. The patient experienced vertigo/balance disturbance (previously reported term dizziness) until 04 Oct 2010, headache until 30 Sep 2010 and the patient was still experiencing otalgia at the time of reporting. It was confirmed that patient was not hospitalized. It was not sure if the patient had ptosis. Outcome was reported as that the patient had not yet recovered.
Follow up report received from physician on 31 Oct 2010 and 08 Nov 2010: The neurological report on 22 Oct 2010 had provided diagnosis of suspected vaccination reaction following administration of meningococcal vaccine. It was reported that the patient was experiencing vertigo/ balance disturbance and slight otalgia with blocked ear sensation bilaterally which was described as cotton-ear feeling began on 23 Sep 2010. Cranial MRI previously performed revealed normal findings. Serology to both Borrelia and Varicella zoster virus (VZV) was respectively unremarkable. Neurologic tests showed unremarkable clinical-neurological condition. Treatment with prednisone 100 mg/day orally was started on 27 Sep 2010. The patient experienced pharyngeal pain on 29 Sep 2010. So an otorhinolaryngology examination was recommended. Antibody tests, chemical tests and hematology tests were normal except for slightly elevated GPT (ALT) of 71 U/L. Symptoms had improved on 01 Oct 2010. The outcome was reported as recovered but otalgia was still recurring from time to time and not yet recovered.
Follow-up report received from the physician on 08 Nov 2010: Diagnosis of 'peripheral facial paresis right-sided' as per anamnesis was made. To investigate lesions on facial nerve anatomy besides the general analysis on other potentially present pathological conditions, imaging examinations were performed on 24 Sep 2010 which showed unremarkable findings corresponding to age showing no hints for brain ischemia, no suspicion of occupying mass and unremarkable results following enhancement. Laboratory examinations performed on 24 Sep 2010 including blood test, C-reactive protein (CRP), thyroid function values (for all, TSH, fT3 and fT4), serum sodium, serum potassium, serum glucose, serum creatinine, glomerular filtration rate, total protein, ALT (GPT), gamma-GT (GGT) and coagulation parameters were likewise all within normal range. Special lab investigations in blood sample of 24 Sep 2010 included normal both serum Borrelia burgdorferi (Bb) IgG antibody level of 22 U/mL and serum Borrelia burgdorferi IgM antibody level of 19 U/mL, thus revealing no hints for acute or chronic Bb-infection. Treponema pallidum particle agglutination (TP-PA) test was found to be negative. Varicella zoster virus (VzV) IgG antibody level was increased

up to 5275 IU/mL and was accompanied by normal VzV IgM antibody level of less than 10.0 IU/mL.
Follow up report received from the patient ((b) (6)) and vaccine adverse event reporting system (VAERS reference number 402523) on 19 Nov 2010 and 30 Nov 2010, respectively: According to follow-up information, this case was found to be a duplicate of PHHY2010DE74470. Hence all the information from case PHHY2010DE74470 was merged in this case and case PHHY2010DE67070 would be deactivated. Following information was merged to this case: The patient had a history of Herpes zoster virus infection, with thoracic localization, eight years ago. The patient stated that the laboratory physician confirmed that Varicella-zoster virus IgG antibody level increased up to 5275 IU/ml and it was fully compatible with the Herpes zoster virus infection the patient had experienced eight years previously. The patient confirmed assessment of outcome as recovered with respect to most symptoms except otalgia which was not yet resolved.
Company assessment:
Serious spontaneous report
Facial paresis [medically significant] assessed as unlisted according to the Core Data Sheet.
The information provided in this individual case does not warrant a change to the Core Data Sheet text. The topic will be monitored closely.
The remaining reported leading events were assessed as non-serious by Novartis Medical Safety Physician.
Chronology suggestive for a causal relationship, however, the other symptoms reported are suggestive of an infection.

PHY2010DE74470:
Combined initial report received from physician via email on 29 Oct 2010 and 03 Nov 2010: This patient was vaccinated with Menveo (quadrivalent conjugated meningococcal ACWY vaccine, batch number not known) on an unspecified date. The site and route of administration were not known. One week following vaccination, the patient experienced facial paresis and vestibular affection (NOS). The outcome and other details of the events were not provided. The physician did not report any seriousness criterion for the suspect vaccination reaction.
Follow up report received from the physician on 19 Nov 2010: According to follow-up information, this case was found to be a duplicate of case PHHY2010DE67070. Therefore information from this case was merged into case PHHY2010DE67070 and this case would be deactivated.
Company assessment:
Serious spontaneous report
Facial paresis [medically significant] assessed as listed in the Core Data Sheet. All spontaneous reports are considered suspected for reporting purposes or in accordance with national regulatory requirements.
The remaining reported leading events were assessed as non-serious by Novartis Medical Safety Physician.
Medical assessment: As this case is a duplicate of case PHHY2010DE67070, case PHHY2010DE74470 will be deactivated.

PHHY2010ID74311:
Combined initial and follow-up report received from a health care professional on 04 Nov 2010 and via National committee for vaccination on 15 Nov 2010: This patient with an unknown medical history was vaccinated Menveo (men a conjugate - crm 197, men c conjugate - crm 197, men w conjugate - crm 197, men y conjugate - crm 197, batch number unknown) intramuscularly on 30 Sep 2010. After vaccination with Menveo, the patient experienced allergic reaction, itchy, fever, skin exfoliation, face edema, fatigue and malaise on 01 Oct 2010. The patient took chlorpheniramine maleate (CTM) (antihistaminic), dexamethasone, paracetamol and salicylic acid on 02 Oct 2010. In between 05 Oct 2010 and 12 Oct 2010, the reaction increased so patient stopped treatment with chlorpheniramine maleate (CTM), dexamethasone, and paracetamol. On 13 Oct 2010, the reactions were worsened and the physician advised to hospitalize but the patient refused. The physician gave antihistaminic (unspecified), ciprofloxacin (antibiotics), chlorpheniramine maleate (CTM) and dexamethasone. On 18 Oct 2010, the reaction was still continued and on (b) (6) (b) (6), the patient was hospitalized due to decrease in consciousness (according to patient's family). On 03 Nov 2010, the patient experienced bone pain and fatigue again. The outcome of the allergic reaction was reported as complete recovery. The causal relationship was under investigation by National committee for vaccination, whether it was related or not.
Company assessment:
Serious spontaneous report
Consciousness decreased, Bone pain [hospitalisation] assessed as unlisted according to the Core Data Sheet. However other alternative causes [underlying conditions] provide a possible explanation for the reported adverse event.
Hypersensitivity, Pyrexia [hospitalisation] assessed as listed in the Core Data Sheet.
Time relation to vaccination of one day could be plausible for a causal relation regarding hypersensitivity.

PHHY2010US47298
Initial report received from a nurse on 15 Jul 2010: This patient was vaccinated with Menveo (meningococcal groups A, C, Y and W-135 oligosaccharide diphtheria CRM197 conjugate vaccine; batch number: unknown) on an unspecified date, the patient concomitantly received hepatitis A vaccine (manufacturer unknown; therefore conservatively considered as Havpur INN). The patient experienced syncopy associated with "seizure like movements". The patient fell and head strucked. The patient was admitted to hospital on an unknown date. The outcome of the events was not reported.
Follow up report received from a physician on 22 Jul 2010: The patient had history of mild aortic regurgitation and syncope (two times). The patient information was updated. The hepatitis A vaccine was confirmed as Havrix (non-Novartis vaccine). CAT scan was performed which was negative. The patient also experienced tonic convulsion. The patient was discharged on an unknown date. The syncope work up was in progress. Final outcome was not reported.
Follow up report received from the physician on 10 Aug 2010: The physician confirmed that ten to fifteen minutes after vaccination, the patient experienced tonic convulsions.
Follow up report received from the physician on 16 Aug 2010: The patient had no history of previous brain injury. There were no syncopal episodes after previous vaccination. The patient was vaccinated with Menveo (lot number: 160004) on 07 Jul 2010. The patient was

diagnosed with closed head trauma secondary to syncope and fever on 07 Jul 2010. Final outcome of the events was not reported.
Company assessment:
Serious spontaneous report
Tonic convulsion, Syncope [hospitalisation] assessed as unlisted according to the Core Data Sheet.
The information provided in this individual case does not warrant a change to the Core Data Sheet text. The topic will be monitored closely.
The remaining reported leading event was assessed as non-serious by Novartis Medical Safety Physician.
Time relation to vaccination of 5 min is plausible for a causal relation.

PHHY2010US71372:
Initial report received from vaccine adverse event reporting system (VAERS 396173) on 25 Oct 2010: This patient was vaccinated with Menveo (men a conjugate - crm 197,men c conjugate - crm 197,men w conjugate - crm 197,men y conjugate - crm 197, batch number unknown) and TdaP (tetanus, diphtheria, pertussis vaccine, batch number unknown) on an unspecified date. On an unspecified date, the patient fainted. Outcome of event was not reported.
Company assessment:
Serious spontaneous report
Syncope [medically significant] assessed as listed in the Core Data Sheet. All spontaneous reports are considered suspected for reporting purposes or in accordance with national regulatory requirements.
Review of available reported data does not allow a proper causality assessment.

1.5 Analysis and conclusion

No increased frequency of already known side effects has been observed. From the serious unexpected adverse experiences during the reporting period, no new safety signal has been seen.

It is concluded that the current safety information for Menveo is sufficient and no changes are required.

2 NARRATIVE DISCUSSION OF ACTIONS TAKEN

During the reporting period there were no actions taken due to safety reasons. A change to the label had been made since the last PAER was submitted and is reflected in the new label. The reason for this change was a clarification to the "2.1 Preparation for Administration" section.
The currently valid package insert is provided in Appendix 3.

3 INDEX LINE LISTINGS

A listing of non-15-alert cases (all serious listed as well as non-serious listed and unlisted cases) having occurred in the United States during the reporting period is provided in Appendix 4.

4 VAERS FORMS

See Appendix 5 for the VAERS forms of all non-15-day alert cases received during the reporting period.

NOVARTIS VACCINES

PERIODIC ADVERSE EXPERIENCE REPORT (QUARTERLY REPORT)

For

ACTIVE SUBSTANCE(S):	**Conjugated oligosaccharides of *Neisseria meningitidis*, serogroups A, C, Y and W-135**
MEDICINAL PRODUCTS COVERED:	**Meningococcal (Serogroups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine, (Menveo®)**
US LICENSE NUMBER	**1751**
SUBMISSION TRACKING NUMBER (STN)	**125300/0**

PERIOD COVERED BY THIS REPORT

From Nov 19, 2010 to Feb 18, 2011 (data lock point)

Date of this report: March 09, 2011

REPORT NUMBER	4
MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:	Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue Cambridge, MA 02139.
NAME AND CONTACT DETAILS OF THE AUTHOR:	Sabine Haertel, MD Pharmacovigilance Novartis Vaccines & Diagnostics GmbH Emil-von-Behring-Str. 76 35041 Marburg, Germany Phone +49 6421 39 2679 Fax +49 6421 39 3662 Email: sabine.haertel@novartis.com
SIGNATURE:	Haertel Sabine Digitally signed by Haertel Sabine DN: cn=Haertel Sabine, ou=people, CR, serialNumber=916895, dc=com, novartis Date: 2011.03.09 10:13:45 +01'00'

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Appendix 1 Listing of all 15-day alert cases submitted to VAERS

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Appendix 6 Literature

1 NARRATIVE SUMMARY AND ANALYSIS

1.1 Introduction and overview

This report summarizes Menveo Adverse Event cases from the US and 15-day alert cases from foreign countries between Nov 19, 2010 to Feb 18, 2011 received by Pharmacovigilance Novartis Vaccines and Diagnostics.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

During the reporting period six 15-day alert reports including (no follow-up report(s)) were submitted to FDA .Two cases occurred in the United States (pharyngitis and cellulitis), one case occurred in Italy (meningism), two cases were reported from Germany (Facial paresis and localized infection) and one case occurred in Austria (pyrexia).

There were 28 cases of non-serious (unlisted and listed) cases, three of which were listed and 25 cases which were unlisted (Appendix 4). Additionally, there were four follow up cases considered non-serious (unlisted).

1.2 Line listing of 15-day alert cases submitted during the reporting period

Appendix 1 includes all 15-day alert cases submitted during the reporting period, identified by manufacturer number, the adverse experience terms, and the date of submission.
During the reporting period six 15-day alert reports were submitted.

1.3 Summary tabulation events displayed by body system

The summary tabulation is provided under Appendix 2. It is ordered by body system and includes all adverse experience terms and counts of occurrences (events) received during the reporting period. As one report can include several terms, the total number of terms is higher than the total number of cases received.

1.4 Clinical significance of 15-day alert reports

In the following all 15-day alert cases are presented according to body system. A narrative description and an evaluation are provided for each case. Evaluation consists of the assessment of expectedness and causality by the company.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

PHHY2010AT77206
A 16 year-old male from Austria was vaccinated with Menveo. On the same day, the patient experienced fever, headache and vaccination site swelling. All events were considered to be known reactions. The patient completely recovered from all the events.

INFECTIONS AND INFESTATIONS

PHHY2010DE83855
A 21-year-old female in Germany with unknown medical history was vaccinated with Menveo. In the evening of the vaccination day, the patient developed erythema with itching at injection site. The subject was diagnosed with vaccination reaction in left upper arm, and a local infection with diffuse panniculitis, an abscess was disregarded. Laboratory results were consistent with the diagnosis. The event was interpreted by physician as fat tissue necrosis possibly induced due to subcutaneous injection. The patient recovered from all events.

PHHY2010US59181
An 18-year US old male was vaccinated with Menveo. One day after vaccination the patient developed a diffuse, red, itchy rash on the face, trunk and limbs of the body. After one month, diagnosis of strep throat with scarlet fever was made. The patient recovered from severe rash one month after onset of symptoms and the outcome of the event sore throat with scarlet fever was reported as condition improving.

PHHY2010US88782
A 48 year-old male in the US with a unremarkable vaccination history (Tdap and Influenza vaccine two months ago), and a medical history of high blood cholesterol and hypertension, taking concomitantly Crestor and Diovan since two months and was vaccinated with Menveo. Approximately 12-24 hours hours after vaccination, the patient began to experience pain and swelling below the injection site. The patient was later diagnosed with cellulitis and a treatment with antibiotics was started. Evaluation of affected Menveo batch did not reveal any deviations from the predefined product specifications. The reporter stated that the alcohol pad used during vaccination was probably recalled from the market. The hospital used only 2 brands of alcohol pads among which one brand was recalled from market.

NERVOUS SYSTEM DISORDERS

PHHY2010DE67070
A 33-year-old male in Germany, who is (b) (6), with a medical history of allergy to house dust mite and pollen and thoracic herpes zoster infection eight years ago, was vaccinated with Menveo. Seven days after vaccination the patient developed facial paresis, ptosis, dizziness (recurrent), headache, otalgia, pharyngeal pain and probably

vertigo/balance disturbance. He was not hospitalized. Cranial MRI, chemical tests and hematology were unremarkable, only GPT was slightly increased. Serology showed evidence for the Herpes zoster virus infection eight years ago but was otherwise unremarkable. A neurological report provided the diagnosis of suspected vaccination reaction following administration of meningococcal vaccine. Later, the diagnosis of 'peripheral facial paresis right-sided' as per anamnesis was made. Treatment with prednisone was started. The outcome was reported as recovered, otalgia resolved two months later.

The reason for a facial palsy may be manyfold (e.g., infections, tumors, autoimmune, traumatic, and others[1]). Due to the close time relationship to vaccination, it cannot be excluded that the vaccination contributed to the onset of the events. A persistent (or latent) infection without symptoms, e.g. the Herpes zoster virus of the face may be co-suspected.

PHHY2011IT03670
A 33-year old female patient in Italy was vaccinated with Menveo and Intanza (influenza virus vaccine,). On the same day, she developed cervico-cephalgic meningeal inflammation with pain at motion of the head. She also developed reddening and swelling at the injection site. Outcome of the events was not reported. The events were assessed as non-serious by the reporter but classified as serious by the company.

1.5 Analysis and conclusion

Therefore no safety measure was considered necessary from these cases presented above.

No increased frequency of already known side effects has been observed. From the serious unexpected adverse experiences during the reporting period, no new safety signal has been seen.

It is concluded that the current safety information for Menveo is sufficient and no changes are required.

2 NARRATIVE DISCUSSION OF ACTIONS TAKEN

During the reporting period there were no actions taken for safety reasons. Changes to the label were made since the last PAER was submitted and are reflected in the new label. The reason for these changes was CBER's approval of Novartis' sBLA seeking an indication in children aged 2-10 years (STN 125300/95).

The currently valid package insert is provided in Appendix 3.

[1] Rath B, Linder T, Cornblath D, Hudson M, Fernandopulle R, Hartmann K, Heininger U, Izurieta H, Killion L, Kokotis P, Oleske J, Vajdy M, Wong V; Brighton Collaboration Bell's Palsy Working Group. All that palsies is not Bell's the need to define Bell's palsy as an adverse event following immunization. Vaccine. 2007 Dec 21;26(1):1 14. Epub 2007 Nov 8.

3 INDEX LINE LISTINGS

A listing of initial and follow-up non-15-day-alert cases (all serious listed as well as non-serious listed and unlisted cases) having occurred in the United States during the reporting period is provided in Appendix 4.

4 VAERS FORMS

Appendix 5 provides the VAERS forms of all cases specified in section 3.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Drug Safety and Epidemiology

Periodic Safety Report for the Period 19 Feb 2011 – 18 May 2011

Menveo® (Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine)

BLA # 125300

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1 Introduction

The Menveo® (Meningococcal (serogroups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine) periodic safety report summarizes the post-marketing safety data for BLA # 125300 received by Novartis Pharmaceuticals Corporation between 19 Feb 2011 and 18 May 2011.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	3	1
Foreign	7	9

- Listings and VAERs forms for all domestic serious/labeled events received during the reporting period.

Table 2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
0	0

- Listings and VAERs forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
54	0

- Listings and VAERs forms for all domestic non-serious/labeled events received during the reporting period.

Table 4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
1	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 20 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, ten were initial reports and ten were follow-up reports.

3.1 Cardiac disorder

PHHO2010US12589 (Clinical trial/HCP): A 16 month old African American male subject with an unknown medical history was enrolled in a phase 3b, open-label, randomized, parallel-group, multi-center study to evaluate the safety of Novartis MenACWY conjugate vaccine (Menveo) when administered with routine infant vaccinations to healthy infants. The subject received his 1st, 2nd 3rd and 4th doses of Menveo on 18 May 2009, 20 Jul 2009, on 21 Sep 2009, and on 22 Mar 2010 respectively. Approximately 4.5 months after the last dose of Novartis MenACWY conjugate vaccine, the subject experienced an upper respiratory infection and four days later developed a febrile seizure. On (b) (6) 2010, the subject experienced sudden epistaxis, syncope, cardiac arrest while in a car, hemorrhaging from the mouth and died five days later on (b) (6). The autopsy revealed a slightly asymmetric skull, slightly focal deep scalp hemorrhage, 2.5 cm area of organizing subdural blood at left parietal dura, left temporal lobe arachnoid cyst of approximately 2 cm, mild laryngeotracheobronchitis with follicular hyperplasia of lymph nodes, Peyer's patches and splenic white pulp. Perimortem laboratory studies during resuscitative effort were consistent with prolonged hypoxic-ischemic condition. No other significant disease or injury was identified. In the opinion of the investigator the arachnoid cyst was congenital and did not cause the death; the leptomeningeal thickening was related to the cyst. Microscopic findings were consistent with the history of recent respiratory illness but were not sufficient to account for the history of sudden unresponsiveness or death. The abnormal laboratory results were consistent with the prolonged cardiovascular collapse. The small organizing subdural blood and the small deep contusions were not sufficient to cause death, how they occurred was unclear. A toxicology examination revealed only the drug atropine used in resuscitation. The investigator concluded that based on the scene circumstances and autopsy findings, as well as a review of medical records and law enforcement investigation, the cause of death is undetermined. The investigator assessed all events as not suspected to be related to the study vaccine.

3.2 General disorders and administration site conditions

PHHY2010AT62397 (Spontaneous report/HCP): A 16 year old female with an unknown medical history was vaccinated with Menveo 0.5ml intramuscularly on 17 Aug 2010, and the next day presented with fever of 38.7°C which was followed with fatigue, arthralgia and headache the following day. The outcome of the events was reported as completely recovered. The events were medically significant and suspected to be related to Menveo.

PHHY2011SE27069 (Spontaneous report/HCP): A 48 year old male with an unknown medical history received Menveo 0.5ml intramuscularly on 02 Dec 2010, and the next day experienced fever greater than 39°C, fatigue, headache and dizziness which required hospitalization. Laboratory tests and brain magnetic imaging resonance (MRI) were negative

for a specific infection. The patient completely recovered after several weeks. The reporter assessed causality as related to Menveo. Concomitant medication included simvastatin.

3.3 Infections and infestations

PHHY2010DE83855 (Spontaneous report/HCP): This report was discussed in the previous periodic safety report for period 19 Nov 2010 to 18 Feb 2010. A 21 year old female in good general and nutritional condition with an unknown medical history was vaccinated with Menveo on 09 Nov 2010 and on (b) (6) the patient was hospitalized and was diagnosed with fat tissue necrosis possibly induced due to subcutaneous injection. Follow-up received during this review period provided no new medical information.

PHHY2011US17356 (Spontaneous report/HCP): An 18 year old female with an unknown medical history was vaccinated on 24 Feb 2011 with Menveo 0.5 ml intramuscularly of the deltoid muscle and Tubersol PPD (tuberculin purified protein) 0.1 ml intradermally for screening of tuberculosis on the same day. The next day the patient developed a medically significant erythematous area with possible cellulitis adjacent to the injection site. The patient was treated with antibiotics. Outcome was reported as improving. Concomitant medications included an unspecified oral contraceptive daily.

3.4 Musculoskeletal and connective tissue disorders

PHHY2011DE15500 (Spontaneous report/HCP): A 55 year old male with a history of herniated discs of the cervical and thoracic spine and drug hypersensitivity was vaccinated on 06 Jul 2010 with Menveo intramuscularly at the right upper arm. On the same day, the patient also received Twinrix E (hepatitis B vaccine) intramuscularly in the right upper arm, Repevax (diphtheria, pertussis, polio, tetanus vaccine) intramuscularly in the left upper arm and Stamaril (yellow fever vaccine) subcutaneously in the left upper arm. Two days later, the patient experienced slight paresthesia in the inner sides of both wrists which was followed the next day with swelling of both wrists and pain in the vertebral spine. On examination, the wrists were minimally swollen and mobility not reduced. The patient was subsequently hospitalized from (b) (6) (b) (6), with suspicion of intervertebral disc prolapse of the cervical spine and carpal tunnel syndrome. Tumor and vaccination damage were excluded. The patient's outcome was reported as recovered. Concomitant medication included L-thyroxine. Vaccination history included receiving Menveo and Twinrix one month earlier.

3.5 Nervous system disorders

PHHY2011AT33130 (Spontaneous report/HCP): An 17 year old male with an unknown medical history was vaccinated with Menveo on 19 Apr 2011 and experienced headache and an unspecified visual field defect of the left eye on the same day, which were medically significant. Visual field defect lasted for 1.5 days; an MRI and CT were negative. Outcome was reported a recovered. Causality was reported as related to the vaccination.

PHHY2011CZ23708 (Spontaneous report/HCP): A 3 year old male was vaccinated on 09 Mar 2011 with Menveo and was hospitalized on (b) (6) after he developed an atypical febrile convulsion, fever and unconsciousness which lasted for five minutes. The patient had undergone diaphragmatic hernia surgery an unspecified time earlier before receiving the

vaccination. The patient recovered from the seizure and causality was assessed as suspected to the vaccine.

PHHY2011US36774 (Spontaneous report/HCP): A 12 year old male with an unknown medical history was vaccinated with Menveo intramuscularly on 25 Apr 2011, and approximately 3-4 hours later, the patient experienced a severe migraine, dizziness, blurriness and continuous emesis which required hospitalization. Outcome was reported as completely recovered.

PHHY2011ID33943 (Spontaneous report/HCP): A patient of unknown age and gender, with a history of asthma was vaccinated with Menveo on 09 Mar 2011, and two days later experienced syncope. Event outcome and causality details were not reported.

3.6 Psychiatric disorders

PHHY2011FR13469 (Spontaneous report/HCP): A 32 year old male with no medical history or allergies was vaccinated with Menveo on 12 Feb 2011. The following day, the patient experienced delirium, hallucinations, which were medically significant, and hot flushes, nausea, vomiting, headache, coated tongue, loss of appetite, chills with a temperature of 39°C, muscular pains flu like symptoms that led to walking difficulty. The patient presented to the emergency room with a fever of 40°C. Urinary bands showed trace of blood and protein in urine. Treatment included paracetamol and the patient's condition improved. Causality was assessed as related to the vaccine.

3.7 Skin and subcutaneous tissue disorders

PHHY2010ID74311 (Spontaneous report/HCP): A male patient with an unknown medical history was vaccinated on 30 Sep 2010 with Menveo intramuscularly and that evening experienced an allergic reaction, itchiness, fever, skin exfoliation, face edema, fatigue and malaise. The patient was treated with chlorpheniramine, dexamethasone, paracetamol and salicylic acid, but the condition worsened five days later and persisted for the next seven days. The patient was subsequently hospitalized for a drug eruption; treatment included dexamethasone, gentamicin, methylprednisolone, azithromycin and neurotropic drips. The outcome of the drug eruption was reported as recovered. The National Committee for Vaccination assessed the drug eruption as a vaccine reaction based on the temporal relationship, but stated that other possibilities may be considered to have caused a worsening of the drug eruption symptoms such as other drugs (ciprofloxacin and paracetamol). The event causality for the drug eruption was assessed as certain.

PHHY2011DE18073 (Spontaneous report/HCP): A 16 year old female with a medical history of acarodermatitis, pruritis, mouth edema, conjunctivitis and lip swelling was vaccinated with Menveo on 17 Feb 2011, and Rabipur (rabies virus vaccine) and Revaxis (diphtheria, tetanus, polio vaccine) intramuscularly. On 20 Feb 2011, the patient developed a cough, rhinitis, sore throat, difficulty swallowing and inflammatory changes at eyes, later followed with lesions of the oral mucosa and swelling of lips. A herpes infection was suspected and treatment with acyclovir and cefixime were initiated. The patient was hospitalized on (b) (6) due to an aggravation of clinical condition. Examination on admission revealed that the patient had reduced general condition, purulent conjunctivitis concerning both eyes, lips that were partially covered with pustules and scabby epithelium and the oral mucosa was partially

covered with aphthous lesions. PCR testing was negative for herpes simplex type I and herpes simplex type II DNA. An x-ray of the thorax revealed signs for beginning infiltration in the pericardial area. A gynecological examination revealed colpitis with reddening of genital mucosa and fluor albus. Ophthalmological examination revealed purulent blepharo conjunctivitis. The patient was hospitalized with stomatitis and conjunctivitis. Due to inflammatory processes of the genital mucosa, a diagnosis of Fuchs' syndrome as a form of Steven Johnson Syndrome (SJS) was made. Athlete's foot was also seen. The patient was treated and the condition improved. The reporting physician stated that Fuchs Syndrome was most probably caused by drugs, herpes simplex or infection with mycoplasma. The clinical symptoms of cough and signs of pneumonia on x-ray were in agreement with an infection of mycoplasma; the initial mycoplasma titer on admission was borderline positive. The outcome was reported as condition unchanged for Steven Johnson syndrome. Further it was stated that the vaccinations might be a cause for the reported symptoms. Vaccination history included Japanese Encephalitis vaccine and Hepatitis A and B vaccine which were received 16 days prior to the onset of events.

4 Co-suspect 15-Day-Alerts (reported to other NDA/BLAs)

There were no reports in which Menveo was listed as a co-suspect medication and reported to another NDA/BLA.

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no actions taken for safety reasons. Changes to the label were made since the last periodic report was submitted and are reflected in the new label. The reason for these changes was CBER's approval of Novartis's BLA for persistence of meningococcal antibodies in adolescents through 21 months following first vaccination with Menveo (STN 125300/49). The currently valid package insert is provided in section 8.0.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

9 VAERS forms and line listings

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Drug Safety and Epidemiology

Periodic Safety Report for the Period 19 May 2011 – 18 Aug 2011

Menveo® (meningococcal (Groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

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Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	1	1
Foreign	8	2

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
0	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
104	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
11	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 12 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, nine

were initial reports and three were follow-up reports. Noteworthy cases will be discussed individually or as a group in the context of specific body systems.

3.1 Eye disorders

PHHY2011AT62754 (Health authority report/HCP): A 15 year old female with a history of allergic bronchial asthma was vaccinated with Menveo on 12 May 2011 and three days later experienced an unspecified eye disorder, visual snow, tearing, severe headache and hypertension with a blood pressure of 163/132 mmHg, requiring hospitalization. The events resolved after three days. The reporter assessed causality as suspected to Menveo. Concomitant medication included formoterol fumarate/budesonide for bronchial asthma.

3.2 Infections and infestations

PHHO2010US06190 (Clinical trial/HCP): A 9 month old male subject with a history of left groin swelling and a deep suppurative lymph node abscess was enrolled in a phase 3b, open-label, randomized, parallel-group, multi-center study to evaluate the safety of Novartis MenACWY conjugate vaccine (Menveo) when administered with routine infant vaccinations to healthy infants. The patient received the first dose of study vaccine on 30 Sep 2009, the second dose on 28 Nov 2009 and the third dose on 27 Jan 2010. The patient received concomitantly the diphtheria/tetanus/pertussis/polio/haemophilus influenzae type B vaccine 27 Jan 2010, hepatitis B virus vaccine on 30 Jan 2010, influenza H1N1 vaccine on 27 Jan 2010 and 13 Mar 2010, influenza vaccine on 30 Jan 2010, pneumococcal conjugate vaccine on 27 Jan 2010 and rotavirus vaccine 27 Jan 2010. On 10 Apr 2010, the patient had experienced a viral syndrome with fever that lasted for five days, followed by a full body, fine pin point rash; the patient received acetaminophen, and the condition had resolved. Ten days later, the patient developed a sudden onset of swelling in the left inguinal region. On examination, the left groin area was found to have a large, non pulsatile inguinal mass with a significant edema and erythema (7cm x 5cm); the area was tender on palpation, indurated and firm with no fluctuance or involvement of the penis. There was erythema in the buttock region with small papules and the area was warm to touch. An ultrasound revealed soft tissue and subcutaneous fat edema and irregular fluid pockets with complex fluid collection. The patient also had adenitis. A diagnosis of left inguinal abscess and left groin cellulitis was made; it was stated that 'it was likely from a necrotic node.' The patient was hospitalized and treated with parenteral antibiotics and an incision and drainage. The drained fluid grew methicillin-resistant staphylococcus aureus (MRSA). The patient made a complete recovery from the viral syndrome, left inguinal abscess and left groin cellulitis; residual palpable scar tissue was noted from the abscess. Vaccination history included diphtheria/tetanus/pertussis/polio/ haemophilus influenzae type B vaccine on 30 Sep 2009 and 28 Nov 2009, hepatitis B virus vaccine on 18 Jul 2009 and 30 Sep 2009, pneumococcal conjugate vaccine on 30 Sep 2009 and 28 Nov 2009 and rotavirus vaccine on 30 Sep 2009 and 28 Nov 2009. Causality was assessed as suspected to the study vaccine by the investigator for the events of cellulitis, inguinal abscess, lymph node abscess from MRSA and necrotic node, but not suspected for the viral syndrome.

PHHY2011AT60468 (Health authority report/HCP): A 32 year old female with an unknown medical history was vaccinated with Menveo intramuscularly on 30 Jun 2011. On the same day, the patient experienced pain in the upper arm and was subsequently hospitalized with a diagnosis of phlegmonous inflammation of the upper arm. C-reactive protein had increased to

12 (units not reported). The patient also presented with meningitis symptoms, which was assessed by a dermatologist to be an unspecific concomitant reaction of the infection. The patient was treated with antibiotics and recovered from phlegmonous inflammation after 17 hours. The events were suspected to be related to Menveo. No other vaccines were administered concomitantly.

PHHY2011CZ42765 (Spontaneous report/HCP): An 11 year old female with allergy to amoxicillin was vaccinated with Menveo intramuscularly on 29 Apr 2011. The next day, the patient developed phlegmon on the side of left arm with painful, medium tough edema and redness involving an area of 10x15 cm. Treatment included cefadroxil, bisulepine, ibuprofen and glucosaminoglycan. Final event outcome was unknown. Vaccination history included a meningitis C vaccine on 29 Oct 2004 and a tick-borne encephalitis vaccine on 25 Feb 2011. The reporter assessed the events as serious and causality as suspected to Menveo.

3.3 Nervous system disorders

PHHO2011PA01204 (Clinical trial/HCP): A 10 month old female subject with a history of a cold was enrolled in a phase 3b, open-label, randomized, parallel-group, multi-center study to evaluate the safety of Novartis MenACWY conjugate vaccine (Menveo) when administered with routine infant vaccinations to healthy infants. The patient received the first dose of study vaccine on 29 Apr 2010, the second dose on 05 Jul 2010 and the third dose on 28 Aug 2010. The patient received concomitantly a diphtheria/tetanus/pertussis/polio/haemophilus influenzae type B vaccine/hepatitis B vaccine and a pneumococcal conjugate vaccine. On 25 Dec 2010, the patient presented with diarrhea, vomiting and loss of appetite which was followed with muscular spasms and eye deviations three days later. Treatment included intravenous fluids, Bacilus Clausii, aluminum hydroxide, and isoprinosine. The patient was hospitalized on (b) (6) due to persisting diarrhea and was diagnosed with gastroenteritis and convulsion with electrolyte imbalance; blood work revealed sodium of 135.4 mmol/l, CO2 of 18 mmol/L, potassium of 4.4 mmol/L and chlorine of 114 mmol/L (normal values were not reported). The patient made a complete recovery from gastroenteritis and was discharged on the same day. Approximately one month later, the patient experienced diarrhea with blood, fever of 39°C, convulsion, hyponatremia (sodium of 131mmol/L) and dehydration. Blood work revealed leukocytosis and parasitology leukocytes were observed in clumps. Treatment included an anti-convulsant. Final outcome was not provided. Vaccination history included a Bacillus Calmette-Guérin vaccine and hepatitis B vaccine on 03 Feb 2010 and a rotavirus vaccine on 29 Apr 2010 and 05 Jul 2010. Causality was assessed as not suspected to the study vaccine by the investigator for the events of convulsion and gastroenteritis.

PHHY2011DE70121 (Spontaneous report/HCP): A 25 year old male with an unknown medical history was vaccinated with Menveo subcutaneously (incorrect route of administration) on 19 May 2011 and a diphtheria/tetanus/pertussis/polio vaccine on 25 May 2011. The following day, the patient presented with Guillain-Barre-Syndrome (GBS) and hypoesthesia of the acra (in context with GBS). Approximately three weeks later, the patient also experienced facial paresis on both sides (in context with GBS). The patient was subsequently hospitalized and an examination of cerebrospinal fluid, electroneurography and autoimmune diagnostic tests were performed; results were not reported and will be collected in a follow-up. The facial paresis resolved after six days. The outcome of the other events was

not reported. Vaccination history included a rabies vaccination on 19 Mar 2008. Causality was not provided.

3.4 Vascular disorders

PHHY2011AT69695 (Spontaneous report/HCP): A 20 year old male with a history of hypotension was vaccinated with Menveo intramuscularly and a rabies virus vaccine on unspecified dates. Five hours after vaccination with Menveo, the patient experienced circulatory weakness with collapse. Event outcome was reported as improving. Causality was not provided.

PHHY2011CZ40496 (Spontaneous report/HCP): A 12 year old male with an unknown medical history was vaccinated with Menveo on an unspecified date. After vaccination, the patient fainted, collapsed and experienced general malaise. Event outcome was reported as recovered. The reporter assessed the events as suspected to Menveo.

PHHY2011IT56696 (Health authority report/HCP): A 22 year old female with an unknown medical history was vaccinated with Menveo and the Japanese encephalitis vaccine on 27 May 2011. The patient developed hypotension and lipothymia on the same day and was treated with caffeine. The outcome was not reported. Causality was reported as possibly related to the vaccinations.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9: MedWatch forms 3500A and line listings, identified as "Cases Sent As FDA 3500As Under Another NDA".

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no actions taken for safety reasons. Changes to the label were not made since the last periodic safety report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Drug Safety and Epidemiology

Periodic Safety Report for the period 19 Aug 2011 – 18 Nov 2011

Menveo® (meningococcal (Groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

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Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, Y and W-135.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	6	4
Foreign	6	5

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
5	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
83	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
22	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 21 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, 12 were initial reports and 9 were follow-up reports.

All cases were discussed individually below in the context of specific system organ class (SOC). A summary of the serious/unlisted events within each SOC are also described below; SOCs that are not summarized did not have any serious/unlisted events reported. Please refer to 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.1 Blood and lymphatic system disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This one adverse event (lymphadenopathy) was a serious unlisted event. There were no reports fatal outcomes associated with this body system.

3.2 Cardiac disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This one adverse event (coronary artery dilatation) was a serious unlisted event; this event is part of PHHO2010CR05755 (Kawasaki's disease) which is presented in the Vascular disorders SOC. There were no reports of fatal outcomes associated with this body system.

3.3 Gastrointestinal disorders

During this review period, a total of 15 adverse events from nine case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were abdominal pain, diarrhea and oral disorder. There were no reports of fatal outcomes associated with this body system.

3.4 General disorders and administration site conditions

During this review period, a total of 96 adverse events from 39 case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were general symptom, inflammation, irritability and pyrexia. There were no reports of fatal outcomes associated with this body system.

PHHO2011GB16789 (Clinical trial/HCP): A 21-year-old male subject with an unknown medical history was enrolled in a phase 3 observer blind randomized, multi-center, controlled study to evaluate the effect of Novartis vaccine's meningococcal B recombinant and MenACWY conjugate vaccines on pharyngeal carriage of N. meningitidis in young adults. The subject received the study vaccination on 23 Oct 2010 and on 06 Dec 2010. Concomitant vaccines included hepatitis A, typhoid and yellow fever; concomitant medication included doxycycline for malaria prophylaxis. The subject (b) (6) (b) (6). On 16 Sep 2011 the subject experienced fever, flu like symptoms and mild diarrhea. On 20 Sep 2011 the symptoms resolved. On 28 Sep 2011 the subject developed fever, cough, sore throat,

hematuria and hospitalized (b) (6) days later. Laboratory findings revealed a negative anti nuclear antibodies (ANA HEp2) test, anti-neutrophil cytoplasmic antigens from cANCA screen (IIF) and pANCA screen(IIF) were negative, the PR3(EIA) was < 1.0 (normal: < 2.0), MPO (EIA phadia) was 1.0 U/ml (normal: < 9.0) and anti glomerular basement membrane (EIA) was negative. The renal ultrasound scan showed the right kidney measuring 10.6cm and the left measuring 11.1cm; cortical depth was preserved. The echogenicity of both kidneys appears to be bright. There were no focal renal lesion, no calcified stone and no hydronephrosis. The bladder appeared normal with no post micturition residue and no ascites. The investigator's conclusion on the kidney bladder ultrasound was that "the appearance of echogenic kidneys carried a wide differential including glomerulonephritis, acute interstitial nephritis with the history of atypical infection". A chest x-ray was normal. On (b) (6), malarial films, blood cultures and blood test for schistostomiasis were normal. The subject was discharged the next day. The subject did not receive any treatment for the events and study vaccination was discontinued due to the events. On 30 Oct 2011, the subject completely recovered from the events. The investigator stated that a possible differential diagnosis was post streptococcal glomerulonephritis or possible IgA nephropathy. The investigator suspected a relationship between the events and the study vaccination although a latency of more than 9 months was reported between the last injection and the onset.

PHHY2011DE51298 (Health authority/HCP): A 51-year-old male patient with an unknown history was vaccinated with first dose of Menveo on 18 May 2011. On the same day, the patient developed fever with severe weakness and vaccination site rash on the entire upper arm, extending to axilla. The patient also experienced swelling and redness at injection site on the same day. Treatment included ibuprofen and ethacridine lactate. Outcome was reported as improving with the weakness reported as ongoing. The patient had tolerated previous unspecified vaccinations well.

3.5 Infections and infestations

During this review period, a total of three adverse events from three case reports were identified under this body system. Of these, there was one serious unlisted event (cellulitis). There were no reports of fatal outcomes associated with this body system.

PHHY2011AT60468 (Health authority report/HCP): This is a follow-up report involving a 32 year old female with an unknown medical history who was vaccinated with Menveo and diagnosed with phlegmonous inflammation of the upper arm and meningitis symptoms on the same day she received the vaccination. The patient recovered from phlegmonous inflammation after 17 hours. The events were suspected to be related to Menveo. Follow-up information reported that the patient was treated with intravenous antibiotics.

3.6 Injury, poisoning and procedural complications

During this review period, a total of 76 adverse events from 74 case reports were identified under this body system. Of these, there was one serious unlisted event (inappropriate schedule of drug administration). There were no reports of fatal outcomes associated with this body system.

PHFR2011GB05747 (Spontaneous report/HCP): A 52-year-old male patient with a history of asthma received a second dose of Menveo less than one week from the first dose. A few days later, the patient’s wife confirmed that the patient had not experienced any adverse events as a

result of the second dose of Menveo. The reporter assessed this case as serious. Outcome was reported as recovered, and causality was assessed as not suspected.

PHHY2011PT76491 (Health authority/HCP): A 10-year-old male patient with an unknown medical history was vaccinated with Menveo on 30 Jul 2011. According to the reporter, the vaccine was wrongly administered because Menveo was indicated for an age of 11 years and above. No adverse event was reported following this administration error. This was considered serious by the Health Authority.

PHHY2011PT76495 (Health authority/HCP): A 6-year-old male patient with an unknown medical history received the first dose of meningococcal vaccine in 2008 and then Menveo on 30 Jul 2011. According to the reporter, the vaccine was wrongly administered because Menveo was indicated for an age of 11 years and above. No adverse event was reported following this administration error. This was considered serious by the Health Authority.

3.7 Metabolism and nutrition disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, there was one serious unlisted event (type 1 diabetes mellitus). There were no reports of fatal outcomes associated with this body system.

PHEH2011US03684 (Spontaneous report/HCP): A 14-year-old male patient with an unknown medical history was vaccinated with Menveo in Aug 2011. Approximately one month later, the patient was diagnosed with type I diabetes mellitus. Outcome was reported as unchanged. Although the information do not allow for a proper causality assessment a temporal relation cannot be excluded. The case will be reassessed when additional information becomes available.

3.8 Musculoskeletal and connective tissue disorders

During this review period, a total of seven adverse events from seven case reports were identified under this body system. Of these, there was one serious unlisted event (pain in extremity). There were no reports of fatal outcomes associated with this body system.

3.9 Nervous system disorders

During this review period, a total of 30 adverse events from 21 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events identified were convulsion, facial paresis, Guillain-Barre Syndrome, hypoesthesia, meningism and syncope. There were no reports of fatal outcomes associated with this body system.

PHEH2011US01456 (Spontaneous report/HCP): A 19-year-old male patient with an unknown medical history was vaccinated with Menveo on an unspecified date and experienced a seizure after vaccination an unspecified time later. The outcome was not reported.

PHEH2011US03474 (Spontaneous report/HCP): A 16-year-old male patient with an unknown history was vaccinated with Menveo and an influenza vaccine on the same day. Following the vaccination, the patient experienced an immediate seizure which lasted for

approximately 10 seconds and syncope. The patient was very nervous prior to the vaccine and had not eaten all day. Causality and event outcome were not reported.

PHEH2011US06998 (Spontaneous report/HCP): A male child of an unknown age and unknown medical history was vaccinated with Menveo and diphtheria/tetanus/pertussis vaccine and “minutes” after the vaccination, the patient experienced a short episode of syncope. Outcome was reported as resolved.

PHEH2011US07000 (Spontaneous report/HCP): An adult female patient with a penicillin allergy was vaccinated with a booster dose of Menveo and “minutes” after vaccination, the patient experienced a short episode of syncope. Outcome was reported as resolved. Vaccination history included administration of Menactra (meningococcal vaccine) which was well tolerated.

PHHY2011DE70121 (Health authority/HCP): This is a follow-up report involving a 25-year-old male patient with an unknown medical history who was vaccinated with Menveo subcutaneously (incorrect route of administration) on 19 May 2011 and with Repevax (diphtheria, tetanus, pertussis and polio vaccine) intramuscularly on 25 May 2011. The patient presented with Guillain-Barre-Syndrome (GBS) and hypoesthesia of the acra (in context with GBS) on 26 May 2011 and facial paresis (also seen in context with GBS) on both sides on 14 Jun 2011. Follow-up information from the health authority contained no new information.

3.10 Psychiatric disorders

During this review period, a total of two adverse events from one case report were identified under this body system. Of these, there was one serious unlisted event (abnormal behavior). There were no reports of fatal outcomes associated with this body system.

PHEH2011US02931 (Spontaneous report/HCP): A 14-years-old female patient with a history of frontal and occipital injury at three months of age, obsessive-compulsive disorder, speech disorder and an abnormal EEG was vaccinated with Menveo on 29 Aug 2011. Within less than 20 minutes after receiving vaccination, the patient developed bizarre behavior (described as laughing, giggling and crying uncontrollably all at same time) for approximately half-an-hour; pulse rate was 132, blood pressure was 100/60, respiratory rate was 42 and pulse oxygen level was 96%. The patient also experienced voluntary shaking of all extremities, was ripping up whatever paper she could get a hold of and kept saying that "she was fine". The patient also complained about pain in her arm. The patient was in the emergency room for two hours before her mental status returned to normal. The patient had a similar episode after the last vaccination with diphtheria/tetanus/pertussis vaccine on 20 Aug 2010 which lasted for ten to fifteen minutes.

3.11 Renal and urinary disorder

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were hematuria and pyuria. There were no reports of fatal outcomes associated with this body system.

3.12 Respiratory, thoracic and mediastinal disorders

During this review period, a total of six adverse events from five case reports were identified under this body system. Of these, there was one serious unlisted event (cough). There were no reports of fatal outcomes associated with this body system.

3.13 Skin and subcutaneous tissue disorders

During this review period, a total of 13 adverse events from 10 case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were erythema and rash. There were no reports of fatal outcomes associated with this body system.

3.14 Vascular disorders

During this review period, a total of three adverse events from three case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were circulatory collapse and Kawasaki's disease. There were no reports of fatal outcomes associated with this body system.

PHHY2011AT69695 (Spontaneous report/HCP): This is a follow-up report involving a 20-year-old male with a history of hypotension who was vaccinated with Menveo intramuscularly and a rabies virus vaccine on unspecified dates. Five hours after vaccination with Menveo, the patient experienced circulatory weakness with collapse. Follow-up information reported that the patient completely recovered after two days following sufficient fluid intake and rest. Causality was reported as suspected.

PHHO2010CR05755 (Clinical trial report/HCP): This 10-week-old male patient was enrolled in a phase 3b, open-label, randomized, parallel-group, multi-center study to evaluate the safety of Novartis MenACWY conjugate vaccine when administered with routine infant vaccinations to healthy infants. The patient received the first dose of study vaccine on 15 Feb 2010 and subsequent doses on 14 Apr 2010 and 10 Jun 2010. The patient received concomitant vaccines, Infantrix (diphtheria, tetanus, pertussis) and Prevnar (pneumococcal conjugate vaccine). On 27 Feb 2010, the patient suffered fever, irritability, abdominal pain and diarrhea. On (b) (6), the patient was admitted to hospital as symptoms continued. The patient underwent laboratory tests for sepsis, an echocardiogram and lumbar puncture. The patient was diagnosed with Kawasaki's disease and treated with cefixime and acetaminophen. On (b) (6), the patient recovered with sequelae and was discharged from hospital the same day. An echocardiogram performed on 22 Mar 2010 revealed dilation of the coronary artery and treated with acetylsalicylic acid. An echocardiogram control was performed on 26 Apr 2010, and a decrease of the coronary artery dilation was observed. On an unspecified date, the patient experienced bilateral conjunctival erythema (unknown if associated with exudate), oral mucosal changes, peripheral extremity changes, rash, cervical lymphadenopathy (unilateral and < 1.5cm diameter), cardiac complications of dilatation of coronary artery and meatitis or sterile pyuria complications. There were no complications of arthralgia, arthritis, aseptic meningitis, gall bladder hydrops, hearing loss, hepatitis or hepatomegaly, iritis or uveitis associated with this event. It was unknown if there were complications of hearing loss, myalgia or myositis. An echocardiogram on 12 Oct 2010 revealed a 3mm dilation of the left coronary artery without an aneurysm and a 2mm dilation of the right coronary artery. The patient experienced sequelae from the event. The investigator

suspected a relationship between the event and study medication. On 06 Jan 2011, the patient underwent an echocardiogram with results showing 'without dilatation of the cavities'. On 15 Mar 2011, the patient was in good health and received varicella vaccine virus (live) and diphtheria/tetanus/pertussis/tetanus/polio/hemophilus influenza vaccine. On 07 Jul 2011 the patient's echocardiogram showed a decrease in the dilation of left coronary artery to 1.9 mm. The investigator reported possible relationship of Kawasaki's disease with the study vaccination due to temporality of the vaccine administration and the onset date of the event.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA".

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no actions taken for safety reasons. Changes to the label were not made since the last periodic safety report was submitted.

(b) (4)

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

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Periodic Safety Report for the period 19 Nov 2011 – 18 Feb 2012

Menveo® (meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for BLA # 125300 received by Novartis Vaccines & Diagnostics and processed by Drug Safety and Epidemiology of Novartis Pharma between 19 Nov 2011 and 18 Feb 2012.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, W-135 and Y.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	3	0
Foreign	5	2
Total	8	2

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
18	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
126	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
59	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 10 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, eight were initial reports and two were follow-up reports (one case had both an initial and a follow-up submission during the reporting period).

All cases were discussed individually below in the context of specific system organ class (SOC). A summary of the serious/unlisted events within each SOC are also described below; SOCs that are not summarized did not have any serious/unlisted events reported. Please refer to 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.1 Blood and lymphatic system disorders

During this review period, a total of three adverse events (AEs) from three case reports were identified under this body system. These three AEs were non-serious unlisted events (lymphadenopathy (3)). There were no reports fatal outcomes associated with this body system.

3.2 Cardiac disorders

During this review period, a total of one AE from one case report was identified under this body system. This one AE (cyanosis) was a non-serious unlisted event. There were no reports of fatal outcomes associated with this body system.

3.3 Ear and labyrinth disorders

During this review period, a total of one AE from one case report was identified under this body system. This one AE (auricular swelling) was a non-serious unlisted event. There were no reports of fatal outcomes associated with this body system.

3.4 Eye disorders

During this review period, a total of two AE from two case reports were identified under this body system. These two AEs (eye swelling and vision blurred) were non-serious unlisted events. There were no reports of fatal outcomes associated with this body system.

3.5 Gastrointestinal disorders

During this review period, a total of 25 AEs from 20 case reports were identified under this body system. Of these, four were serious listed events (lip swelling, nausea, odynophagia and vomiting). There were no serious unlisted events and no reports of fatal outcomes associated with this body system.

3.6 General disorders and administration site conditions

During this review period, a total of 241 AEs from 99 case reports were identified under this body system. Of these, five were serious unlisted events. The serious unlisted events

identified were chest pain (2), inflammation, vaccination site nodule and vaccination site pyrexia. There were no reports of fatal outcomes associated with this body system.

The four 15-day reports belonging to this SOC are presented below:

PHHY2011BR109343 / Vaccination site ulcer (spontaneous non-HCP report/ Initial report): A 35-year-old female subject was vaccinated with Menveo (batch M10120, manufacture date Jul 2010 and expiry date Jun 2012) into the left arm, intramuscularly on 09 Dec 2011. The first reactions started from 09 Dec 2011 to 10 Dec 2011. She presented with chills, pain in her whole body, legs pain, headache, column pain and tiredness. As corrective treatment, she used caffeine/ metamizole/ orphenadrine citrate at a dose of "two tablets a day for every four hours" without medical orientation. On 10 Dec 2011 in the morning, she presented with malaise and she noticed that there were two small balls below the site where the needle was inserted. She "supposed that was with fever" and she decided to administer dipyrone at a dose of 40 drops two or three times. On 10 Dec 2011, according to the physician from the vaccination clinic, she started the administration of acetaminophen/ caffeine/ carisoprodol/ diclofenac at 2:00 pm and used six tablets between 10 Dec 2011 and 11 Dec 2011. The physician oriented that there was an application of warm water at application site of the vaccine and believed that the application of warm water worsened her condition, the redness spread due to the warm water. On 12 Dec 2011, the subject returned to the vaccination clinic where she was diagnosed with a **local ulcer** by another physician and was prescribed cefalexin 500 mg every six hours for 10 days. The causality and outcome were not reported.

PHHY2011FR113343 / Pain (spontaneous HCP report from French HA/ Initial report): An 18-year-old male subject was vaccinated with Menveo (batch M20097) intramuscularly and Vaxigrip (influenza vaccine, manufacturer unknown, batch H8320-1) intramuscularly on 06 Dec 2011. On 08 Dec 2011, he experienced **pain**, fever over 38°C, headaches and dizziness. He was admitted to the ER and was unavailable to work. He recovered 24 hours later without sequelae. The French HA assessed the causality as probable for Menveo and Vaxigrip.

PHHY2011HU106926 / Chest pain (spontaneous HCP report from Hungarian HA/ Initial and Follow-up report): A 15-year-old female adolescent received the following vaccinations without any post-vaccination reactions: Meningococcal vaccine (batch R0266-3) on 29 Mar 2000, Menjugate (meningococcal group C-CRM_{197} conjugate) on 23 Apr 2003, Havrix (hepatitis A, inactivated) on 16 Nov 2007, and 19 Jun 2008, Fluval P (monovalent influenza vaccine) on 12 Nov 2009 and Cervarix (human papillomavirus bivalent (types 16 and 18), recombinant) on 03 Dec 2010 and 05 Jan 2011. She was vaccinated with Menveo (batch M10069) on 18 Nov 2011. On 19 Nov 2011, one day after vaccination, she experienced strong headache, nuchal pain, pain in the left arm and **chest pain radiating to the left shoulder blade**. She was unable to tolerate light (photosensitivity). She took one paracetamol tablet and had a high fluid intake. The outcome was reported as reaction resolved on 20 Nov 2011 except the pain in the lower arm region. It was reported that the method of vaccine transportation, storage temperature and circumstances before use were appropriate according to the investigation report provided by National Public Health and Medical Officer Service.

PHHY2012BR005883 / Chest pain (spontaneous non-HCP report/ Initial report): An 8-year-old male child was vaccinated with Menveo (batch unknown, expiry date Aug 2012) in the arm on 19 Jan 2012. Thirty (30) minutes after vaccination, he complained of **pain in the middle of his chest**, in his shoulder and muscle pain in entire body. The maximum pain

occurred seven hours after vaccination. He was admitted to the ER and dipyrone was applied into his vein (it was not applied together with hydration solution).The outcome was reported as recovered.

3.7 Infections and infestations

During this review period, a total of five AEs from five case reports were identified under this body system. Of these, there was one serious unlisted event (cellulitis). There were no reports of fatal outcomes associated with this body system.

The two 15-day reports belonging to this SOC are presented below:

PHEH2011US07069 / Vaccination site cellulitis (spontaneous HCP report/ Initial report): An 11-year-old male child was vaccinated with Menveo (batch A10058) intramuscularly into his right deltoid on 10 Oct 2011. On the same day, he was also vaccinated with Boostrix (diphtheria, tetanus, acellular pertussis vaccine, other manufacturer, batch AC528074AA) intramuscularly. On 11 Oct 2011, he developed **cellulitis at the injection site** (6 x 8 inches area). He required treatment with steroids. The outcome was reported as recovered.

PHHY2011AT60468 / Cellulitis (spontaneous HCP report from Austrian HA/ Follow-up report): A 32-year-old female subject was vaccinated with Menveo (batch A/X10099) intramuscularly on 30 Jun 2011. No other vaccines were administered concomitantly. For 15 minutes after vaccination, nothing conspicuous was observed, and the vaccine was also optically unsuspicious. On the same day after vaccination, she experienced pain in the upper arm. She went to day clinic because of the event and was eventually hospitalized with a diagnosis of **phlegmonous inflammation at upper arm**. C-reactive protein was increased to 12 (units not reported). She also presented with meningitis symptoms, which were assessed to be an unspecific concomitant reaction of the infection by a dermatologist. She was treated with intravenous antibiotics and she recovered from phlegmonous inflammation after 17 hours. The events were suspected to be related to Menveo. The Austrian HA stated it was not possible to obtain additional data.

3.8 Injury, poisoning and procedural complications

During this review period, a total of 82 AEs from 80 case reports were identified under this body system. Of these, there were three serious listed events (fall (2) and head injury). There were no serious unlisted events and no reports of fatal outcomes associated with this body system.

3.9 Investigations

During this review period, a total of five AEs from five case reports were identified under this body system. Of these, there were four non-serious unlisted events (blood pressure decreased (2), body temperature decreased and heart rate increased) and one non-serious listed event (body temperature increased). There were no reports of fatal outcomes associated with this body system.

3.10 Metabolism and nutrition disorders

During this review period, a total of three AEs from three case reports were identified under this body system. All three AEs (decreased appetite) were non-serious. There were no reports of fatal outcomes associated with this body system.

3.11 Musculoskeletal and connective tissue disorders

During this review period, a total of 24 AEs from 16 case reports were identified under this body system. Of these, there were two serious unlisted event (musculoskeletal pain and pain in extremity). There were no reports of fatal outcomes associated with this body system.

The 15-day report belonging to this SOC is presented below:

PHHY2011FR105769 / Myalgia (spontaneous HCP report from French HA/ Initial report): A 19-year-old female subject was vaccinated with Menveo (batch M10097) in the right shoulder intramuscularly on 02 Nov 2011 and was also vaccinated with Vaxigrip (influenza vaccine, split virion, inactivated, batch H8318-1) in the left shoulder intramuscularly on 02 Nov 2011. On the same day, she experienced headache, stiffness, nausea, **myalgia** and vomiting leading to unavailability of the patient for one day. The outcome was favorable after two days. The reporter suspected Menveo to be related to the events.

3.12 Nervous system disorders

During this review period, a total of 59 AEs from 45 case reports were identified under this body system. Of these, two were serious unlisted events (meningism and syncope). There were no reports of fatal outcomes associated with this body system.

The 15-day report belonging to this SOC is presented below:

PHEH2011US009548 / Syncope (spontaneous HCP report/ Initial report): A male subject of unknown age was previously vaccinated with Menveo and tolerated it well. He was vaccinated Menveo (batch M10051) intramuscularly on unspecified date. After vaccination, he experienced **syncope**. He became normal within 5-10 minutes after syncope. The outcome and causality were not reported.

3.13 Respiratory, thoracic and mediastinal disorders

During this review period, a total of eight AEs from five case reports were identified under this body system. Of these, there were four serious listed events (dyspnea, pharyngeal edema and throat tightness). There were no serious unlisted events and no reports of fatal outcomes associated with this body system.

The 15-day report belonging to this SOC is presented below:

PHEH2012US002131 / Pharyngeal edema (spontaneous HCP report/ Initial report): A 19-year-old female subject was vaccinated with Menveo (batch M10123) intramuscularly on 23 Jan 2012. Ten minutes after vaccination, she experienced **swelling in her throat**, it hurt to touch the throat and it hurt to swallow. In the night, she was crying because she felt like her throat was closing up and not able to breath. She took diphenhydramine last night but it did not help. The outcome and causality were not reported.

3.14 Skin and subcutaneous tissue disorders

During this review period, a total of 61 AEs from 43 case reports were identified under this body system. Of these, one was a serious unlisted event (erythema). There were no reports of fatal outcomes associated with this body system.

3.15 Vascular disorders

During this review period, a total of six AEs from six case reports were identified under this body system. The six AEs were serious unlisted events (pallor (6)). There were no reports of fatal outcomes associated with this body system.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA". There was no such case in the reporting period.

5 Estimate of patient exposure

During the period from 01 Dec 2011 to 29 Feb 2012, a total of (b) (4) doses of Menveo were sold in the United States. Therefore, the patient exposure in the United States during the reporting period is estimated to be around (b) (4) subjects.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no regulatory actions taken for safety reasons. Changes to the label were not made since the last periodic safety report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

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Periodic Safety Report for the period 19 Feb 2012 – 18 May 2012

Menveo® (meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for BLA # 125300 received by Novartis Vaccines & Diagnostics (NVD) and processed by Drug Safety and Epidemiology of Novartis Pharma between 19 Feb 2012 and 18 May 2012.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, W-135 and Y.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	13	2
Foreign	10	12
Total	23	14

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
3	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
91	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
26	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 37 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, 23 were initial reports and 14 were follow-up reports.

All cases were discussed individually below in the context of specific system organ class (SOC). A summary of the serious/unlisted events within each SOC are also described below; SOCs that are not summarized did not have any serious/unlisted events reported. Please refer to 'Tabulation by System Organ Class (SOC) for All Events Reported' for detailed listing of all reported events.

3.1 Blood and lymphatic system disorders

During this review period, a total of one adverse event from one case report was identified under this body system. The one adverse event was a serious unlisted event (lymphadenitis). There were no reports fatal outcomes associated with this body system. This one report is a 15-day report that was classified under this SOC by leading event and is presented below.

PHHY2012FR036177 / Lymphadenitis (Spontaneous report/HCP): A 34-year-old male with an unspecified medical history was vaccinated with Menveo (batch number: M10145) intramuscularly on 26 Mar 2012. On the same day after vaccination, the patient presented with inflammation (up to 5cm), pain at injection site, lymphadenitis, fever and asthenia which led to three days of work stop. Biological work up did not identify an etiology. The patient completely recovered within three days. The French Health Authority assessed the causal relationship with Menveo as possible.

3.2 Cardiac disorders

During this review period, a total of three adverse events from one case report were identified under this body system. All three were serious unlisted events. The serious unlisted events identified were myocarditis, pericardial effusion and pericarditis. There were no reports of fatal outcomes associated with this body system. This one report is a 15-day report that was classified under this SOC by leading event and is presented below.

PHHY2012NO028491 / Myocarditis (Spontaneous report/HCP): An 18-year-old female with an unspecified medical history was vaccinated with Menveo (batch number: unknown) on 05 Mar 2012. (b) (6), the patient was hospitalized due to myocarditis, pericarditis, myalgia, malaise, chest pain, shivering and headache. Laboratory investigations performed on unspecified dates in Mar 2012 included transthoracic echocardiography which revealed increased pericardial fluid in apical and lateral aspect of right ventricle, C-reactive protein was at 128, 134 and 9 (units not provided), urinalysis revealed presence of leucocytes (2+) and ketones (1+), troponin I was at 2578, 8273 and 538 (units unspecified), X-ray thorax was normal, CK-MB was at 16.9 and 31.2 (units not provided) and CK was at 194 (unit not provided). On (b) (6), ECG revealed temporary ST elevation. On (b) (6), the ECG normalized. The outcome of events myocarditis, pericarditis, malaise, and chest pain was reported as recovering when the patient was discharged on (b) (6) The outcome of

events myalgia, shivering and headache was reported as recovered the day after being discharged on (b) (6) . The causality of these events was not reported.

Pericarditis and myocarditis were reported although the signs described in the narrative are only in favor of pericarditis. A follow-up of the case is tentatively trying to clarify the myocarditis diagnosis (enzyme increased and EKG are compatible with the pericarditis alone).

3.3 Ear and labyrinth disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This event was a non-serious listed event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.4 Eye disorders

During this review period, a total of six adverse events from six case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were photophobia, vision blurred, and visual impairment. The case reports containing these events will be discussed in the General disorders and administration site conditions, Immune system disorders and Nervous system disorders SOCs by leading event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.5 Gastrointestinal disorders

During this review period, a total of 18 adverse events from 13 case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were abdominal pain lower and oral mucosal blistering. The case reports containing these events will be discussed in the Immune system disorders and Skin and subcutaneous tissue disorders SOCs by leading event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.6 General disorders and administration site conditions

During this review period, a total of 130 adverse events from 51 case reports were identified under this body system. Of these, 19 were serious unlisted events. The serious unlisted events identified were chest pain, chills, inflammation, malaise, vaccination site erythema, vaccination site induration, vaccination site pain, vaccinations site pruritis, vaccination site swelling and vaccination site warmth. There were no reports of fatal outcomes associated with this body system. There was one 15-day report belonging to this SOC and is presented below.

PHHY2012NO020245 / Malaise (Spontaneous report/HCP): An 18-year-old female with a medical history of allergy to IgE against nuts, dog, cat and birch, left sided tinnitus, chronic dizziness since childhood, syncope, asthma, headache, pituitary adenoma, hearing reduced, sleep problem and otitis was vaccinated with Menveo (batch number: X11020) at a dose of 0.5ml on 10 Feb 2012. On 12 Feb 2012, the patient experienced "rotatory and nautical dizziness, aggravated loss of consciousness, photophobia aggravated, vomiting aggravated, headache aggravated and nausea aggravated." The symptoms experienced by the patient after vaccination had been reported as aggravation of symptoms that have been going on for years.

(b) (6) after vaccination, the patient was hospitalized for a day due to sickness. A lumbar puncture, MR caput and blood test revealed no pathology. Results from microbiologic tests and electrophoresis were unknown at the time. The patient was treated with paracetamol and metoclopramide. On an unspecified date, the patient was discharged from the hospital without medication. Outcome was not reported. The Norwegian Medicines Agency reported the event was possibly related to the treatment with Menveo.

3.7 Immune system disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, one was a serious unlisted event (autoimmune disorder). There were no reports of fatal outcomes associated with this body system. Both reports belonged to this SOC and are presented below.

PHEH2012US008356 / Autoimmune disorder (Spontaneous report/HCP): A female child with an unknown medical history was vaccinated with Menveo (batch number: unknown) intramuscularly on 21 Feb 2012. On the same day, the patient was also vaccinated with Tdap vaccine (diphtheria, tetanus, and pertussis vaccine). Approximately one week after vaccination, the patient began to experience adverse visual effects and assessed to have near vision of 2200 and far vision of 20/20. The physician stated that the patient was able to see but unable to read and believed that this was an autoimmune reaction of the lens in both eyes. It was reported that they could not find anything on microscopic examination. The symptoms were continuing at the time of this report. Causality was not provided.

The reported event was designated as auto-immune disorder but characterized by visual disturbance. A follow-up in order to clarify the signs in favor of auto-immune disorder is ongoing.

PHFR2012GB001155 / Hypersensitivity (Spontaneous report/HCP): A 5 years, 10 months old male child with an unknown medical history had a vaccination history including administration of hepatitis A, hepatitis B and typhoid which were well tolerated. The patient was vaccinated with Menveo (batch number: M10146) on 02 Feb 2012 and complained of a red, swollen, painful right arm on 03 Feb 2012. Treatment included paracetamol, ibuprofen and application of ice. On 04 Feb 2012, the patient had discomfort of the forehead and mouth and had lower abdominal pain. Urinalysis was negative. The patient also experienced swelling of the right cheek, face and upper lip. Treatment included prednisolone after which the swelling resolved. The patient was admitted to the emergency department for observation on an unspecified date. The patient had no respiratory problems or urticaria. The arm still showed a localized reaction. The patient was given chlorphenamine and unspecified steroids as treatment and was discharged the following day. It was reported that Menveo was the cause of allergic reaction and that the patient had not yet gone to an allergy clinic. The outcome of facial swelling and lip swelling were reported as complete recovery, the localized reaction of arm remained unchanged and discomfort of forehead and mouth, abdominal pain and allergic reaction were not reported. Causality was not reported.

3.8 Infections and infestations

During this review period, a total of 12 adverse events from 11 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted

events identified were cellulitis, cellulitis staphylococcal and vaccination site cellulitis. Among those 11 cases with possible cellulitis or vaccination site infection, nine different batches of Menveo were used. (only two cases in Brazil were using the same batch M11036 and two cases in the US were using the batch A10054). There were no reports of fatal outcomes associated with this body system. There were 11 reports which were 15-day reports belonging to this SOC and are presented below.

PHEH2011US07069 / Vaccination site cellulitis (Spontaneous report/HCP): This is a follow-up report with no new medical information involving an 11-year-old male child who was vaccinated with Menveo (batch number: A10058) intramuscularly and Boostrix (diphtheria, tetanus, acellular pertussis vaccine, other manufacturer, batch AC528074AA) intramuscularly on the same day and developed cellulitis at the injection site the next day. This report was described in the previous periodic report.

PHHY2011AT60468 / Cellulitis (Spontaneous report/ HCP): This is a follow-up report with no new medical information involving a 32-year-old female who was vaccinated with Menveo (batch number: A/X10099) who was diagnosis of phlegmonous inflammation at upper arm. This report was described in the previous periodic report.

PHEH2012US007908 / Vaccination site infection (Spontaneous report/HCP): A 25-year-old female with an unknown medical history was vaccinated with only the MenCWY-135 liquid conjugate component of Menveo (batch number: M11061) intramuscularly on 05 Apr 2012 and did not receive the MenA lyophilized conjugate. This maladministration was noted on 06 Apr 2012 and Menveo (batch number: M11041) was re-administered through unspecified route and site on 11 Apr 2012. It was reported that on an unspecified date, the patient's arm became sore, tender and red and subsequently diagnosed with an infection at the vaccination site. Treatment included antibiotics. The outcome of the event was reported as recovered with sequelae. The causality of the events was assessed as suspected to vaccine administration.

PHHY2011US94960 / Vaccination site cellulitis (Spontaneous report/HCP): A 30-year-old female with a medical history of allergies and low immune system was vaccinated with Menveo in the left arm (batch number A10051) and pneumococcal polysaccharide vaccine (manufactured by Merck, batch number: 0595AA) in the right arm on 25 Aug 2011. The patient had a swollen arm at the injection site which was very warm and sore to the touch with redness at the injection site (left or right arm not reported) on 26 Aug 2011. The patient visited two physicians who confirmed cellulitis (7x8 cm). The patient recovered on unspecified date. Concomitant medications included montelukast, cetirizine and cefdinir. Causality was not reported.

PHHY2012BR014045 / Vaccination site cellulitis (Spontaneous report/non-HCP): A 47-year-old male was vaccinated with Menveo (batch number: M11036) 0.5 ml, intramuscularly into the deltoid muscle of arm (unspecified as to which arm) on 08 Feb 2012. The patient did not receive other vaccine doses on the same day of the application of Menveo and did not experience adverse events with previous vaccinations. On 09 Feb 2012, the patient's whole body was covered with "red stains" and the patient experienced pain in the vaccinated arm, a thick palate and the application site had the appearance of necrosis. Cellulitis at the vaccination site was diagnosed and treated with acid mucopolysaccharide polysulphate. On 15 Feb 2012, the cellulitis was "huge." As of 15 Feb 2012, the cellulitis persisted and the palate

remained thick (described as “mouth was large”). The causality of the events was not reported.

PHHY2012BR014054 / Vaccination site cellulitis (Spontaneous report/non-HCP): A male patient of unknown age with an unknown medical history received Menveo (batch number: M11036) intramuscularly in deltoid muscle of arm (unspecified as to which arm) on 08 Feb 2012. The patient did not receive other vaccine doses on the same day of the application of Menveo. On 09 Feb 2012, the patient became ill and experienced cellulitis at the vaccination site, pain and stains throughout the body. Treatment included ceftriaxone. On 16 Feb 2012, the patient condition was improving. Causality was not reported.

PHHY2012NL032441 / Cellulitis staphylococcal (Spontaneous report/HCP): An adult female patient with no past medical history or family history was vaccinated with Menveo (batch number: M10104) into the right upper arm on 22 Feb 2012. On 23 Feb 2012, the patient experienced cellulitis along with painful, swollen and red upper arm. It was reported that the patient was hospitalized (b) (6) days later with signs of cellulitis. Treatment included an unspecified antibiotic given intravenously, ice packs and other unspecified medications. Approximately one week after vaccine administration, the patient was discharged. An unspecified time later, microbiological culture was performed and showed the presence of an unspecified staphylococcus; it was reported that "it concerned staphylococcus cellulitis". Physical findings and investigations were not available at the time of this report. The patient recovered on an unknown date. Duration of the event was reported to be one week. Causality was assessed as possible due to temporal association and location of the event at the site of administration. The patient was not taking any concomitant medications at the time of the event. The Dutch Health Authority reported that no further information was available.

PHHY2012US010341 / Cellulitis (Spontaneous report/HCP): An 11-year-old female patient with an unknown medical history was vaccinated with Menveo vaccine (batch number: M10058) in to the right arm, along with seasonal influenza vaccine (other manufacturer, batch number: AFLUA611A) into the left arm, with HPV4 vaccine (human papilloma virus vaccine, other manufacturer, batch number: 0477AA) into the right arm and with Tdap vaccine (diphtheria, tetanus and acellular pertussis, other manufacturer, batch number: AC52B048AC) into the left arm on 02 Dec 2011. On the same day after vaccination, the patient developed cellulitis. The final outcome was reported as condition unchanged as on 05 Dec 2011. Causality was not reported.

PHHY2012US010520 / Vaccination site cellulitis (Spontaneous report/HCP): A 14-year-old female with an unknown medical history was vaccinated with Menveo (batch number: A10054) intramuscularly on to right arm, FLUN vaccine (influenza vaccine, other manufacturer, batch number: YL2069) through intranasal route and human papilloma virus quadrivalent vaccine (other manufacturer, batch number: 1317AA) intramuscularly on to left arm on 29 Nov 2011. On 30 Nov 2011, the patient experienced right upper arm redness, itching, hot to touch, induration 10-12 cm, cellulitis and an unspecified local reaction. Treatment included ice application, diphenhydramine and cephalexin. The outcome of the events was reported as complete recovery as of 01 Dec 2011. Concomitant medication included sertraline. Causality was not reported.

PHHY2012US010523 / Vaccination site cellulitis (Spontaneous report/HCP): An 11-year-old male with an unknown medical history was vaccinated with Menveo (batch number: A10054) intramuscularly on to right arm and diphtheria/tetanus/acellular pertussis vaccine (other manufacturer, batch number: C3828AA) intramuscularly on to left arm on 29 Nov 2011. On 30 Nov 2011, the patient experienced redness, warm to touch, itching, induration 8cm x 6.8 cm, cellulitis and local reaction to the right upper arm. Treatment included the application of ice, diphenhydramine and cephalexin. The outcome of the events was reported as complete recovery as of 01 Dec 2011. Causality was not reported.

PHHY2012US028891 / Vaccination site cellulitis (Spontaneous report/HCP): An 11-year-old male was vaccinated with Menveo (batch number: M10123) intramuscularly in the left arm on 05 Jan 2012. The patient was also vaccinated with a second dose of Fluzone vaccine (other manufacturer, batch number: U4118AA, seasonal influenza vaccine) intramuscularly in the right arm and Boostrix vaccine (other manufacture, batch number: AC62B072EA, diphtheria, tetanus and acellular pertussis) intramuscularly in the right arm on 05 Jan 2012. On 06 Jan 2012, the patient experienced cellulitis in the left deltoid area and redness at right deltoid area. Treatment included cephalexin. The outcome of the events reported as recovered. Causality was not reported.

3.9 Injury, poisoning and procedural complications

During this review period, a total of 81adverse events from 79 case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were head injury and open wound. The case reports containing these events will be discussed in the Nervous disorders and Skin and subcutaneous tissue disorders SOCs by leading event. There were no reports of fatal outcomes associated with this body system. There were two reports which were 15-day reports belonging to this SOC and are presented below.

PHHY2011PT76491 / Drug administered to patient of inappropriate age (Spontaneous report/HCP): A 10-year-old male child with an unknown medical history was vaccinated with Menveo (batch number: M10092) on 30 Jul 2011. With a correct prescription by the physician, the vaccine was wrongly administered because the vaccine is indicated for age of 11 years and above. The reporter confirmed that no adverse event occurred due to the medication error.

PHHY2011PT76495 / Drug administered to patient of inappropriate age (Spontaneous report/HCP): A 6-year-old male child with an unknown medical history was administered with the first dose of meningococcal vaccine (different manufacturer) in 2008. On 30 Jul 2011, the patient was vaccinated with Menveo (batch number: M10092). With a correct prescription by the physician, the vaccine was wrongly administered because the vaccine is indicated for age of 11 years and above. The health authority confirmed that no adverse event occurred due to the medication error.

3.10 Investigations

During this review period, a total of one adverse event from one case report was identified under this body system. The one event was a serious unlisted event (CSF pressure increased).

There were no reports of fatal outcomes. There was one 15-day report belonging to this SOC and is presented below.

PHEH2012US005261 / Intracranial pressure increased (Spontaneous report/HCP): A 17-year-old female with an unknown medical history was previously vaccinated with Menactra (meningococcal vaccine from another manufacturer, batch number: unspecified) on 23 Jun 2008 which was well tolerated. The patient was vaccinated with second dose of Menveo (batch number: M10127B) intramuscularly on to left deltoid on 23 Feb 2012. On 27 Feb 2012, the patient experienced blurred vision, headache, pain on the right side of neck and numbness on fourth and fifth right fingers and arm. It was reported that subsequently the patient also experienced tingling of the right arm. A history of injury was not reported. Magnetic resonance imaging (MRI) without contrast of brain was negative. It was reported that MRI with contrast was performed and the findings were compatible with intracranial hypertension. The patient was admitted in hospital for spinal tap and the pressure was “up” and drainage was performed. The outcome of the event was reported as condition improving and causality assessed as possibly related to vaccine administration.

3.11 Metabolism and nutrition disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Both events were non-serious listed events. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.12 Musculoskeletal and connective tissue disorders

During this review period, a total of 13 adverse events from 10 case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were muscular weakness, myalgia, neck pain and pain in extremity. There were no reports of fatal outcomes associated with this body system. The one 15-day report belonging to this SOC is presented below.

PHHY2012AT031819 / Muscular weakness (Spontaneous report/HCP): A 12-year-old female with an unknown medical history was vaccinated with Menveo (batch number M1011) intramuscularly on to an unspecified site on 28 Mar 2012. One hour after vaccination, the patient experienced flushing and weakness of lower extremities and was hospitalized. Outcome was reported as condition resolved. Causality was reported as suspected to Menveo.

3.13 Nervous system disorders

During this review period, a total of 36 adverse events from 22 case reports were identified under this body system. Of these, 15 were serious unlisted events. The serious unlisted events identified were convulsion, Guillain-Barre syndrome, headache, hypoasthesia, hyporeflexia, intracranial pressure increased, loss of consciousness, meningism, myelitis transverse, paresthesia, presyncope, syncope and tonic clonic movements. There were no reports of fatal outcomes associated with this body system. There were six reports which were 15-day reports belonging to this SOC and are presented below.

PHEH2012US007219 / Syncope (Spontaneous report/HCP): An 11-year-old male child was vaccinated with Menveo (batch number: unknown) intramuscularly and Tdap (diphtheria,

tetanus and acellular pertussis; other manufacturer) on an unspecified date. The patient felt "sick to his stomach" within five minutes after vaccination and placed his head down at his knees for a little bit and the stomach ache and nausea went away. Within ten minutes after vaccination, the patient fainted and hit the back of the head on the floor. Treatment included ice and oxygen. The patient went home and slept “for hours;” dizziness at night was reported. The patient completely recovered the next day. The reporter suspected the events were related to Menveo and Tdap.

PHEH2012US007397 / Presyncope (Spontaneous report/HCP): An 11-year-old male with an unknown medical history was vaccinated with Menveo (batch number: A10130/ X10130) intramuscularly and with Gardasil (human papilloma virus vaccine, other manufacturer, batch number: unspecified) on 20 Mar 2012. It was reported that the patient became shaky after receiving the vaccinations and experienced a near fainting episode on 20 Mar 2012. The patient completely recovered on the same day. Causality was not reported.

PHEH2012US008954 / Convulsion (Spontaneous report/HCP): A male patient of unknown age with an unknown medical history was vaccinated with Menveo (batch number: M11041) intramuscularly at an unspecified site on 10 Mar 2012. It was reported that the patient subsequently experienced a seizure. The patient experienced a fainting episode with tonic-clonic movements within minutes after vaccination. The condition improved within ten minutes. Causality was not reported.

PHHY2011US94896 / Grand mal convulsion (Spontaneous report/HCP): This is a follow-up with no new medical information involving a 12-year-old male who was a healthy child with an unspecified medical history. The patient was vaccinated with Menveo (batch number: A10051) intramuscularly in the left arm on 11 Aug 2011. The patient developed generalized tonic-clonic seizure with uncertain etiology on 17 Aug 2011. The patient required emergency medical attention. A basic metabolic panel and a brain MRI were performed, but results were not reported. The outcome was reported as a complete recovery. Causality was not reported.

PHHY2012GR039427 / Myelitis transverse (Spontaneous report/HCP): A 13-year-old male patient with a medical history negative for neurological diseases was vaccinated with Menveo (batch number: not reported) through an unspecified route and site on 04 May 2012. On 05 May 2012, the patient experienced right lower limb claudication and was hospitalized the (b) (6) . Twenty hours after hospitalization, the patient’s patella reflexes and achilles tendon reflexes were found to be almost unresponsive. An electromyogram revealed that one parameter was abnormal (not specified). Guillain Barre syndrome was suspected and treatment with gamma globulin on (b) (6) was started. An MRI without contrast media was negative for abnormalities. Findings from an MRI with contrast media (performed on an unspecified date) induced a suspicion of transverse myelitis. Additionally, the patient experienced urinary incontinence that required cathetering. The outcome of the events was not reported. The physician assessed that Menveo was unlikely to be related to the symptoms.

PHHY2012NO024702 / Meningism (Spontaneous report/HCP): A 17-year-old female with an unknown medical history was vaccinated with Menveo (batch number: M11020) at a dose of 0.5 ml at an unspecified site on 16 Feb 2012. On an unknown date after vaccination, the patient was hospitalized twice for photophobia, headache and meningism. Bacterial meningitis was excluded. The symptoms were interpreted as possible complications after

Menveo vaccination. The outcome was reported as condition improving. Causality was not reported.

3.14 Psychiatric disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This event was a non-serious unlisted event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.15 Renal and urinary disorders

During this review period, a total of three adverse events from two case reports were identified under this body system. There was one serious unlisted event (urinary incontinence). The case report containing this event will be discussed in the Nervous system disorders SOC, by their leading event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.16 Respiratory, thoracic and mediastinal disorders

During this review period, a total of three adverse events from two case reports were identified under this body system. All events were non-serious unlisted events. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.17 Skin and subcutaneous tissue disorders

During this review period, a total of 19 adverse events from 15 case reports were identified under this body system. Of these, there was only one serious unlisted event (Stevens-Johnson syndrome). There were no reports of fatal outcomes associated with this body system. The one 15-day report belonging to this SOC is presented below.

PHHY2012US038128 / Stevens-Johnson syndrome (Spontaneous report/HCP): A 23-year-old female with drug allergies to sulfamethoxazole/trimethoprim and penicillin and mushrooms was vaccinated with Menveo (batch number: M10126A) intramuscularly into the left arm on 05 Jan 2012. On 13 Jan 2012, the patient developed blisters in mouth and was diagnosed with Steven Johnson Syndrome in the hospital. Finger wounds were treated with unspecified antibiotics. The patient recovered completely on an unspecified date. Causality was not reported.

It was called Stevens-Johnson syndrome but with only blisters in mouth in the narrative. Follow-up is ongoing with FDA to get more information about other signs such as cutaneous, genital and ocular signs.

3.18 Vascular disorders

During this review period, a total of three adverse events from three case reports were identified under this body system. Of these, there were two serious unlisted events. The serious unlisted events identified were flushing and intermittent claudication. The case reports containing these events will be discussed in the Musculoskeletal and connective disorders and Nervous system disorders SOCs, by their leading event. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA". There was no such case in the reporting period.

5 Estimate of patient exposure

During the period from 01 Mar 2012 to 31 May 2012, a total of (b) (4) doses of Menveo were sold in the United States. Therefore, the patient exposure in the United States during the reporting period is estimated to be around (b) (4) subjects.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no regulatory actions taken for safety reasons. Changes to the label were not made since the last periodic safety report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

A first case of Stevens-Johnson Syndrome was reported in Germany in 2011. A second suspicion of Stevens-Johnson in the US was reported in this reporting period. This second case is ongoing for a follow-up and confirmation on the diagnosis. NVD asked to the FDA to help on the follow-up because the case was reported in the VAERS database. Therefore NVD do not have access to a follow-up.

However, NVD decided to retain the existing verbiage regarding bullous conditions in the Menveo Core Safety Information of the company. NVD will follow the diligence procedures to obtain the information needed to adjudicate and attribute the second reports of possible SJS However, based on the first case, NVD is revisiting the local labels and in particular the US Product Information, to ensure that they are consistent with the Menveo CSI. Outside the Stevens-Johnson Syndrome and based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Drug Safety and Epidemiology

Periodic Safety Report for the period 19-May-2012 – 18-Aug-2012

Menveo® (meningococcal (groups A,C,Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

Author(s): M. Malley, RN

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1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for BLA# 125300 received by Novartis Pharmaceuticals Corporation between 19-May-2012 and 18-Aug-2012.

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2 Summary of case reports

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- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

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	Total initial reports submitted	Total follow-up reports submitted
Domestic	4	3
Foreign	16	7

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
13	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
136	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
48	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 30 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, 20 were initial reports and 10 were follow-up reports.

All cases are discussed individually below in the context of specific body system organ class (SOC). A summary of the serious/unlisted events within each SOC are also described below; SOCs that are not summarized did not have any serious/unlisted events reported. Please refer to 'Tabulation by Body System of All Events Reported' for detailed listing of all events.

3.1 Blood and lymphatic system disorders

During this review period, a total of four adverse events from four case reports were identified under this body system. Of these, two were serious unlisted events (lymphadenitis and lymphadenopathy). There were no reported fatal outcomes associated with this body system.

There were two 15-day reports identified under this body system presented below:

PHHY2012FR044912 / Lymphadenitis (health authority report/HCP): A 26-year-old male with unknown medical history and unknown concomitant medications received Menveo intramuscularly (unknown dose or batch number) and one day later developed pain at the injection site, **lymphadenitis**, fever, headache and asthenia. Three days after onset, the events were reported as recovered. The health authority assessed the events as disability and not related to treatment with Menveo.

PHHY2012FR055461 / Lymphadenopathy (health authority report/HCP): A 38-year-old female with unreported medical history or concomitant medications received a booster dose of Menveo (unknown dose, batch number M10145) along with co-suspect drug Stamaril (yellow fever, other manufacturer, batch number G5771) and on the same day developed fever, headache and **cervical adenopathy**. The event outcome was not reported. It was reported that "another etiology was not ruled out". No other information was reported. The health authority assessed the events as serious and the causality as unlikely to both suspect drugs.

3.2 Cardiac disorders

During this review period, a total of four adverse events from two case reports were identified under this body system. All four were serious unlisted events. The serious unlisted events identified were myocarditis, myopericarditis, pericardial effusion and pericarditis. There were no reported fatal outcomes associated with this body system.

There were two 15-day reports identified under this body system presented below:

PHHY2012NO028491 / Myocarditis, Pericarditis, Pericardial Effusion (health authority report/HCP): This is a follow-up report regarding an 18-year-old female with unreported medical history and concomitant medications who received Menveo (unknown dose, unknown batch number) and on the same day was hospitalized due to **myocarditis**, **pericarditis**, myalgia, malaise, chest pain, shivering and headache. A transthoracic echocardiography revealed increased **pericardial fluid** in right ventricle. An electrocardiogram initially showed ST elevation but a repeat echocardiogram was normal.

She was discharged from the hospital with no bacterial or viral findings. At the time of discharge the events were reported as recovering. The causality of the chest pain, shivering, headache, malaise, pericarditis and myalgia were reported as possible. The causality of the remaining events was not reported. Pericarditis and myocarditis were reported although the signs described in the narrative are only in favor of pericarditis (enzyme increased and EKG are compatible with the pericarditis alone). The primary reporter could not be contacted and therefore further follow-up could not be obtained. The quality assurance department reported the concerned Menveo batch was manufactured in accordance with approved internal procedures and in compliance with current good manufacturing practices (cGMP).

PHHY2012US058747 / Myopericarditis (literature report/HCP): A 17-year-old male without history of angina pectoris, cocaine abuse, hyperlipidemia, congenital heart disease, autoimmune disorder, recent flu-like illness, diarrhea, respiratory symptoms suggestive of an infectious syndrome and no previous travel was vaccinated with meningococcal conjugate (manufacturer unknown, batch number unknown), hepatitis A vaccine (manufacturer unknown) and DTaP (diphtheria, tetanus and acellular pertussis vaccine, manufacturer unknown). It was the first time he was ever vaccinated with meningococcal or hepatitis A vaccine. The following day he developed diffuse arthralgia, intermittent retrosternal chest pain and low grade fever and was admitted to the hospital. His physical exam was negative but an electrocardiogram showed diffuse ST-segment elevation and elevated cardiac enzymes. A chest radiograph and echocardiogram were normal. Rectal and nasopharyngeal swabs were negative for adenovirus and entero-virus. Lyme immunoglobulin (IgG/IgM), cytomegalovirus IgG, Epstein-Barr virus capsid IgM antibody, antinuclear antibody and anti-DS DNA screens were all negative. Over the 24 hours in the hospital the cardiac enzymes level of Troponin 1 continued to increase and a cardiac MRI was positive for myocarditis. Four days later he was discharged from the hospital after the cardiac enzymes decreased. He was discharged with treatment of indomethacin. Within one week of onset of the symptoms, serum cardiac enzymes, C-reactive protein and electrocardiogram were normal. At three weeks post discharge his electrocardiogram showed T wave inversion. At 10 weeks post hospitalization, he remained asymptomatic with normal electrocardiogram and decreased area of contract enhancement on the MRI. The authors wrote the progression of the electrocardiogram changes were associated with **myopericarditis**. The possibility of a viral etiology could not be definitely excluded however the negative viral serology and the absence of symptoms make this a less likely possibility.

3.3 Ear and labyrinth disorders

During this review period a total of two adverse events from two case reports were identified under this body system. Of these, one was a serious unlisted event of hyperacusis. There were no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.4 Eye disorders

During this reporting period a total of 11 adverse events from 11 case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were photophobia (2) and vision blurred. There were no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.5 Gastrointestinal disorders

During this reporting period a total of 22 adverse events from 16 cases were identified under this body system. Of these, one adverse event (nausea) was identified as a serious unlisted event. There were no fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below:

PHHY2012AT058114 / Nausea (spontaneous/HCP): An 11-year-old female with no known allergies, chronic or autoimmune diseases or blood coagulation disorders was vaccinated with Menveo 0.5 ml (batch number: N10140) and later the same day experienced cephalgia, vertigo and **nausea** requiring evaluation at the hospital. She was later discharged on the same day after blood pressure control, hydration, and "bedding". Treatments rendered were not specified. The outcome of the events were reported as complete recovery and suspected to be related to vaccination with Menveo.

3.6 General disorders and administration site conditions

During this reporting period a total of 173 adverse events from 77 case reports were identified under this body system. Of these, 11 were serious unlisted events. The serious unlisted events were identified as chest pain, chills, gait disturbance, malaise, edema peripheral, pyrexia, vaccination site erythema and vaccination site swelling. There were no fatal outcomes associated with this body system.

There were three 15-day reports identified under this body system presented below:

PHFR2012GB003420 / Edema peripheral (spontaneous report/HCP): A 63-year-old female, with no reported medical history or concomitant medications, was vaccinated with Menveo (unknown dose) (batch number: unknown if A11007, expiry date Jan 2013 or X11007, expiry date Jun 2013) and two days later her **arm was painful, red and swollen**. Her HCP thought it was an infection and treated with unspecified antibiotics. However she did not improve and was therefore hospitalized for four days and treated with intravenous antibiotics (unspecified). At the time of the report she was 80% recovered but her arm was still painful. The causality of the events was not reported.

PHHY2012FR068514 / Pyrexia (health authority report/HCP): A 20-year-old male patient with unspecified medical history was vaccinated with Menveo (unknown dose) (batch number: M10136) along with co-suspect drug Priorix (measles, mumps and rubella virus; batch number A69CC891A). After an unknown period of time he developed local pain, **fever**, headache and nausea leading to two days of "unavailability". No other information was reported and therefore due to lack of information the health authority reported the patient had not recovered. The health authority assessed the events as medically significant and unlikely related to Menveo and Priorix.

PHHY2012IT064997 / Injection site urticaria (spontaneous report/HCP): An adult female of unknown age and medical history received one dose of Menveo (unknown dose) subcutaneously and three hours later complained of a **wheal at the injection** site of greater than 5 cm. She was admitted to the hospital (so specifics reported) and was discharged with unspecified antibiotics and cortisone as treatment. The HCP reported there was likely a human error involved due to incorrect administration of the vaccine via subcutaneous route.

The outcome of the event was not reported and no further information regarding causality was reported.

3.7 Infections and infestations

During this review period, a total of four adverse events from four case reports were identified under this body system. Of these, there were two serious unlisted events. The two serious unlisted events were infection and orchitis. There were no fatal outcomes associated with this body system.

There were three 15-day reports identified under this body system presented below:

PHEH2012US012268 / Infection (spontaneous report/HCP): A patient of unknown age, gender, medical history or concomitant medications was vaccinated with Menveo (unknown dose) (batch number: M11071, expiry date Dec 2013) via unspecified route and within three days developed redness and swelling of a 10cm diameter at the injection site. There was no pus. The HCP treated it as an **infection** with Augmentin (amoxicillin sodium, clavulanate potassium). The outcome of the event was not reported and a causality assessment was not reported. The Novartis quality assurance department indicated the batch review of M11071 was manufactured in accordance with approved internal procedures and in compliance with current good manufacturing practices (cGMP) requirements.

PHHY2012FR055430 / Orchitis (health authority report/HCP): A 36-year-old male, with unreported medical history or concomitant medications, was vaccinated with Menveo (unknown dose) (batch number: M10114) intramuscularly and the following day developed a fever, headache and **orchitis** leading to "unavailability" for 10 days. Another etiology was not ruled out (no specifics reported). The health authority assessed this as medically significant and assessed causality as unlikely.

PHEH2012US007908 / Vaccination site infection (spontaneous report/ HCP): This is a follow-up report regarding a 25-year-old female who was vaccinated with only the MenCWY-135 liquid conjugate component of Menveo (unknown dose) (batch number: M11061) intramuscularly. The maladministration was noted the following day and she was re-vaccinated with Menveo correctly (batch number: M11041). After an unspecified period of time her arm became sore, tender and red. Her HCP diagnosed an **infection at the vaccination site** and treated her with unspecified antibiotics. She recovered with sequalae (unspecified) and the causality was reported as suspected to vaccine administration. The follow-up information to this case was received from the Novartis quality assurance department indicating the concerned batch number M11061 was manufactured in accordance with approved internal procedures and in compliance with current good manufacturing practices (cGMP) requirements.

3.8 Injury, poisoning and procedural complications

During this reporting period, a total of 118 adverse events from 116 case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events were drug administered to patient of inappropriate age and wrong drug administered. There were no reports of fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below (containing both the serious unlisted events noted):

PHEH2012US010030 / Wrong drug administered and **Drug administered to patient of inappropriate age** (spontaneous report/HCP): **An 11-month-old male baby was inadvertently vaccinated with Menveo** 0.5ml intramuscularly (batch number: X10057, expiry date Feb 2013). The baby was supposed to have received MMR (measles, mumps, rubella) and not Menveo. He was hospitalized on an unknown date with no specifics reported. No adverse event was reported following the administration error.

3.9 Investigations

During this reporting period, a total of 13 adverse events from seven case reports were identified under this body system. Of these, seven were serious unlisted events. The seven serious unlisted events were blood alkaline phosphatase increased, blood creatine phosphokinase MB increased, blood glucose increased, C-reactive protein increased, CSF pressure increased, cardiac enzyme increased, electrocardiogram ST segment elevation. There were no reports of fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below:

PHHY2012NO065037 / Blood alkaline phosphate increased (health authority report/ HCP): An 18-year-old male with no reported concomitant medications but a vaccination history in 2008 of feeling warm, throat closure, hyperventilation, cold sweat and pallor after receiving Twinrix (hepatitis A and B vaccine) was vaccinated with Menveo 0.5ml (batch number: M10008) and approximately one minute after vaccination he experienced a feeling of warmth in his whole body. He became pale, had cold sweating, had a feeling of throat closure and hyperventilated. His pulse rate ranged from 65 – 80 during this time. His blood pressure measured 84/42 initially and 10 minutes later it was 94/46. His blood pressure subsequently increased to 112/57 and 143/80. His oxygen saturation was 100% and **blood alkaline phosphatase was 238** (normal value not reported). He received Adrenaline (epinephrine), Solu-cortef (hydrocortisone sodium succinate) and oxygen at the time, and was then transferred to the hospital for observation and further treatment with cetirizine and systemic prednisolone. He was released five hours later with complete recovery. The event was considered an anaphylactic reaction. The causality was assessed as suspected.

3.10 Musculoskeletal and connective tissue disorders

During this review period, a total of 47 adverse events from 31 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events were muscle atrophy, muscular weakness, musculoskeletal stiffness (2), myalgia and neck pain (2). There were no reports of fatal outcomes associated with this body system.

There were three 15-day reports identified under this body system presented below:

PHHY2012FR041829 / Musculoskeletal stiffness (health authority report/HCP): This is a follow-up report regarding a 52-year-old female (b) (6) who was vaccinated with Stamaril (yellow fever vaccine) (batch number: G5771-1) intramuscularly and six days later was vaccinated with Menveo (unknown dose) (batch number: M11027) in the same arm she received Stamaril. Four days after the Menveo vaccination she developed paresthesia type

pain in left arm and shoulder, **stiffness** in nape of neck, headache and photophobia followed by fever with sweats a few day later. Twelve days later the events continued and a biological work up was normal and well as the neurological exam. Within days of the exam, the events began to resolve and completely resolved the following month. The health authority assessed the seriousness as medically significant and the causality as unlikely related to either vaccine.

PHHY2012FR059844 / Myalgia (health authority report/HCP): A 27-year-old male with an unspecified medical history received booster doses of Menveo (unknown dose) (batch number: M10114) intramuscularly, Revaxis (other manufacturer diphtheria, tetanus poliomyelitis; batch number H0041) and Typhim VI (other manufacturer salmonella typhi polyamides; batch number G0569) and nine hours later developed a local reaction of **pain** and inflammation at the injection site along with fever, headache and stiffness. Two days later the patient recovered. The health authority assessed the fever, headache, **myalgia**, and pain as medically significant and the causality to Menveo and the other vaccines as possible.

PHHY2012FR068516 / Myalgia (health authority report/HCP): A 20-year-old female with an unspecified medical history was vaccinated with Menveo (unknown dose) (batch number: M10145) intramuscularly and on the same day developed local inflammation of 5 cm along with **myalgia**. The HCP reported that an etiology other than the Menveo was possible (not specified). No other information was reported. Due to the lack of information the health authority reported the outcome of the events as not yet recovered, medically significant and unlikely related to Menveo.

3.11 Nervous system disorders

During this reporting period, a total of 65 adverse events from 43 case reports were identified under this body system. Of these, 14 were serious unlisted events. The serious unlisted events were central nervous system lesion, dizziness, dysstasia, extensor plantar response, headache (2), hypoesthesia (3), hyporeflexia, intracranial pressure increased, meningism, myelitis transverse and paresthesia. There were no reports of fatal outcome associated with this body system.

There were six 15-day reports identified under this body system presented below:

PHEH2012US005261 / Intracranial pressure increased (spontaneous report/HCP): This is a follow-up report regarding a 17-year-old female whose medical history and concomitant medications were not reported. She did have a vaccination history of receiving Menactra (other manufacturer) in 2008 and it was well tolerated. She was vaccinated with the 2nd dose of Menveo (unknown dose) (batch number: M10127B) intramuscularly and four days later developed blurred vision, headache, pain on right side of neck and numbness on fourth and fifth right fingers and arm. Subsequently she developed tingling in her right arm. There was no history of injury. Magnetic resonance imaging (MRI) with and without contrast had findings compatible with **intracranial hypertension**. She was admitted to the hospital for a spinal tap “and pressure was up”. The outcome of the events was reported as unknown and the causality assessed as possible.

PHHY2012DE043574 / Syncope (spontaneous report/HCP): A 21-year-old female with unknown current condition or concomitant medications and no history of neurological diseases or cramps was vaccinated with Menveo (unknown dose) (batch number: A11091). It

was reported "a small amount of vaccine was lost before the vaccination". On the same day, she had a vasovagal reaction with **fainting**. During the fainting her eyes showed movements "similar to movements seen during cramp attacks". No other signs of cramping occurred. The outcome was reported as complete recovery after one minute and the causality was not assessed.

PHHY2012DE064440 / Hypoesthesia (health authority report/HCP): A 26-year-old female with no reported past medical history but vaccination history included recent vaccination with FSME Immun Adult (tick-born encephalitis vaccine, other manufacturer) and two doses of Rabipur (rabies vaccine, unknown batch number) all tolerated well. Thirteen days after the second dose of Rabipur she was vaccinated with Menveo (unknown dose) (batch number: A1037) along with Typhim VI (typhoid vaccine other manufacturer batch G0531-2) and on the same day developed myalgia, injection site redness, vaccination site warmth, tingling of extremity, dizziness, sweating attacks, and swelling of shoulder and left upper arm. Two days later she developed **hypoesthesia** of the left shoulder spreading to cervical area, lasting for one hour. Therefore she was hospitalized for one day. Blood tests revealed C-reactive protein (CRP) of 6.55mg/dl and lymphocytes of 14.9% (normal values not reported). An abdominal ultrasound and echocardiography were normal and results of CT scan of the thorax and electrocardiogram were not provided. The C-reactive protein dropped significantly on day of discharge. No other information was reported. The patient completely recovered on an unknown date.

PHHY2012GR039427 / Myelitis transverse (spontaneous report/HCP): A 13-year-old male with no reported current conditions or concomitant medications and negative history of neurological diseases was vaccinated with Menveo (unknown dose or batch number) and less than 24 hours later he developed right lower leg claudication and weakness in right leg with limping causing hospitalization (very short period of time between the vaccination and the myelitis transverse onset). The following day he developed severe weakness in left leg, bladder difficulties and incontinence requiring a urinary catheter. His patella reflexes and Achilles tendon reflexes were almost unresponsive and "several reflexes were not released". One parameter of the electromyogram was abnormal (not specified). MRI without contrast was negative. Guillain-Barre Syndrome was suspected and he started treatment with intravenous gamma globulin. A second MRI revealed some lesions in the spinal cord (level of thoracic vertebra 11-12) and cerebral spinal exam showed no infection. He was diagnosed with **transverse myelitis** of the lumbar section of the spinal cord and was treated with glucocorticosteroids. His symptoms improved greatly with ongoing treatment. He was hospitalized for a total of 13 days. Fifty days after discharge he continued to improve in his walking but continued to suffer specific muscle deficiencies of both legs. The HCPs caring for him were now unclear if his diagnosis was Guillain-Barre or transverse myelitis. The reporting HCP assessed the causality as unlikely to Menveo.

PHHY2012GR058822 / Hypoesthesia (spontaneous report/non-HCP): A female child of unspecified age and no reported medical history was vaccinated with Menveo (unknown dose or batch number) intramuscularly and on the same day after the vaccination developed **neck numbness**, **upper and lower extremity numbness** and headache. The following day she was hospitalized and released one day later. The patient's mother reported she had an intense reaction at the injection site, was afraid and displayed psychosomatic symptoms on the same side of the body as the injection. The day after discharge her neurological exams were

negative and she was improving. The mother reported the HCP stated Menveo was suspected for the events since the child was examined prior to the vaccination and was free of medical history.

PHHY2012NO024702 / Meningism (health authority report/HCP): This is a follow-up report regarding a 17-year-old female with allergy to Ventolin (salbutamol), current use of oral contraceptive Mercilon, and family history of infarct of the heart in father and migraines with sister who was vaccinated with Menveo 0.5ml (batch number M11020) and five days later was hospitalized for 2 days for **meningism**. Her symptoms began five days after vaccinations with fever and headache. The headache pain was aggravated with movement and tenderness when knocking on her forehead. Two days after onset on the symptoms, she then presented with neck stiffness, neck pain, nausea when turning her head, photophobia, sound sensitivity, light sensitivity and dry cough. Initially the events were thought to be caused by muscular pain, vaccine or a virus. Meningitis was not suspected. She was treated with Afipran (metoclopramide hydrochloride) and Pinex forte (codeine phosphate paracetamol). The day after discharge she had swelling of the face and rash on hands. Two days following discharge she had the previous symptoms again and subsequently recovered. On an unknown date she again had a new episode of headache and cough with purulent expectorate. During a neurological exam signs of **meningism** were found but without neck stiffness or other neurological findings. Two months after vaccination, she again had a sore, stiff neck and shoulder muscles but without signs of meningeal irritation or neck stiffness. The health authority assessed the events as serious and causality as suspected to Menveo.

3.12 Psychiatric disorders

During this reporting period, a total of four adverse events from two case reports were identified under this body system. Of these, there were three serious unlisted events. The serious unlisted events were anxiety, insomnia, and paranoia. There were no reports of fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below (containing all three serious unlisted events noted):

PHEH2012US016064 / Paranoia, anxiety, and insomnia (spontaneous report/HCP): A 23-year-old male, with unreported medical history or concomitant medications, was vaccinated with Menveo (unknown dose) (batch number: X11064) intramuscularly and on the same day he developed **paranoia** and was **anxious**. He also had bleeding gums after brushing his teeth and was **not able to fall asleep at night**. No other information was provided including outcome or causality assessment.

3.13 Renal and urinary disorders

During this reporting period there were six adverse events from four case reports identified under this body system. Of these, three were serious unlisted events. The serious unlisted events were bladder dysfunction, urinary incontinence and IgA nephropathy. There were no reports of fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below:

PHHO2011GB16789 / IgA nephropathy (clinical trial/HCP): This is a follow-up report of a 21-year-old male subject without any reported medical history who was enrolled in study (b) (6), A Phase 3 Observer blind, multi-center, controlled study to evaluate the effect of Novartis vaccine's Meningococcal B recombinant and MenACWY conjugate vaccines on pharyngeal carriage of neisseria meningitides in young adults. Concomitant vaccines included hepatitis A, typhoid and yellow fever. Concomitant medications included doxycycline for malarial prophylaxis. The subject started (b) (6) (b) (6). The subject (b) (6). The subject received the study vaccination on 23 Oct 2010 and on 06 Dec 2010 (the year of these vaccinations are accurate as written) (unknown dosing or batch numbers). On 16 Sep 2011, the subject experienced fever, flu like symptoms and mild diarrhea. On 20 Sep 2011, these symptoms were resolved. On 28 Sep 2011, the subject developed fever, cough, sore throat and hematuria. It was mentioned that the events occurred after the episodes of upper respiratory tract problems. On (b) (6), the subject was hospitalized due to the events. On the same day of hospitalization the lab reports showed the anti-nuclear antibodies (ANA HEp2) test was negative, anti-neutrophil cytoplasmic antigens showed cANCA screen (IIF) and pANCA screen (IIF) were negative, the PR3 (EIA) was less than 1.0(normal less than 2.0), MPO (EIA phadia) was 1.0 U/ml (normal value less than 9.0) and anti-glomerular basement membrane (EIA) was negative. The renal ultrasound scan showed the right kidney measures 10.6cm and the left measures 11.1cm and the cortical depth was preserved. The echogenicity of both kidneys appears to be bright. No focal renal lesion, no calcified stone and no hydronephrosis were seen. The appearance of the bladder was normal with no post micturition residue and no ascites on the visualized images. The investigator's conclusion for the ultrasound kidney bladder was stated as "the appearance of echogenic kidneys carried a wide differential including glomerulonephritis, acute interstitial nephritis with the history of atypical infection". The chest x-ray was normal. On (b) (6), the subject's malarial films, blood culture and blood test for schistostomiasis were normal. The subject did not receive any treatment for the events. Treatment with the study vaccination was discontinued due to the events. On 03 Oct 2011 the subject recovered completely from fever, cough and hematuria. (b) (6), the subject was discharged from the hospital. The investigator also stated the possible differential diagnosis was post streptococcal glomerulonephritis or possible IgA nephropathy. The investigator reported the subject will remain under care of nephrologist. On an unspecified date the subject was diagnosed with **IgA nephropathy**. It was mentioned that the subject had a recurrent event (IgA nephropathy) following an episode of tonsillitis on 25 Apr 2012. The event occurred after the episodes of upper respiratory tract problems. On an unspecified date, the subject's kidney function test was normal. The follow-up information changed the outcome of the event IgA nephropathy to condition unchanged at the time of report, the events (fever and cough) were considered serious (hospitalization) by the investigator, the event IgA nephropathy was considered serious (hospitalization and medically significant) by the investigator and the investigator did not suspect a relationship between the events and the study vaccination.

3.14 Respiratory, thoracic and mediastinal disorders

During this reporting period, a total of 10 adverse events from eight case reports were identified under this body system. Of these, there were two serious unlisted events (cough

and productive cough). There were no reports of fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.15 Skin and subcutaneous tissue disorders

During this reporting period, a total of 55 adverse events from 38 case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events were Henoch-Schonlein purpura and hyperhidrosis (2). There were no reports of fatal outcomes associated with this body system.

There was one 15-day report identified under this body system presented below:

PHHY2012DE068192 / Henoch-Schonlein purpura (health authority/HCP): A 12-year-old male with no reported medical history or concomitant medications was vaccinated with Menveo (unknown dose) (batch number: A11025) intramuscularly and 5 days later presented with **Henoch-Schonlein purpura**. He was not hospitalized and 18 days after onset he "had not yet recovered". No other information was reported other than the HCPs causality assessment of suspected to Menveo.

3.16 Vascular disorders

During this reporting period, a total of nine adverse events from eight case reports were identified under this body system. Of these, two were serious unlisted events (circulatory collapse and intermittent claudication).

There was one 15-day report identified under this body system presented below:

PHHY2012AT037723 / Circulatory collapse (spontaneous report/HCP): A 12-year-old female with negative medical history for allergies, chronic diseases, autoimmune disease or any blood coagulation disorders and no concomitant medications was vaccinated with Menveo 0.5ml (batch number: N10140) intramuscularly. On the same day she had circulatory collapse and was hospitalized. She fully recovered and when discharged after blood pressure control, hydration and "bedding". No specific information was provided regarding treatments or hospitalization. The HCP reported causality as suspected to Menveo.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA". There were no such cases in this reporting period.

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no regulatory actions taken for safety reasons. Changes to the label were not made since the last periodic report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo® US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

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Drug Safety and Epidemiology

Periodic Safety Report for the period 19 Aug 2012 – 18 Nov 2012

Menveo® (meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for BLA # 125300 received by Novartis Vaccines & Diagnostics (NVD) and processed by Drug Safety and Epidemiology of Novartis Pharma between 19 Aug 2012 and 18 Nov 2012.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, W-135 and Y.

An incident was identified, which affected the Marketing Authorization Holder's pharmacovigilance procedure to retrieve and scan publicly available data from the United States (US) post-marketing safety surveillance database Vaccine Adverse Event Reporting System (VAERS) for safety information pertaining to NVD products. A retrospective check revealed that 94 Menveo VAERS cases had not been identified between Nov 2010 and Nov 2011 and therefore, had not been entered in the MAH's safety database. These 94 VAERS 2010-2011 backlog cases (22 serious and 72 non-serious) have since been entered into the MAH's safety database. A cumulative medical assessment based on the analysis of all serious 2010-2011 VAERS backlog cases for Menveo did not reveal any indication for a change in the benefit/risk ratio. During this review period, it was discovered that these 94 cases were reported in earlier Menveo USPRs from 2012, however the description of this incident was not included with the prior Menveo USPRs and therefore summarized now in this report.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	5	1
Foreign	13	3
Total	18	4

- Listings and VAERS forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
21	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
120	0

- Listings and VAERS forms for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
73	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 22 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, 18 were initial reports and four were follow-up reports. There were 22 15-day alerts involving 20 cases.

A summary of the serious/unlisted events within each SOC is also described below; SOCs that are not summarized did not have any serious/unlisted events reported. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.1 Blood and lymphatic system disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This event was a serious unlisted event (lymphadenopathy). There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.2 Cardiac disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, none were serious unlisted events. There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.3 Ear and labyrinth disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, none were serious unlisted events. There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.4 Eye disorders

During this review period, a total of five adverse events from four case reports were identified under this body system. Of these, two were serious unlisted events (eye discharge, eye swelling). There were no reports of fatal outcomes.

There was one 15-day report classified under this SOC by leading event and presented below:

PHHY2012BR083475 / Eye swelling (Spontaneous report/HCP): A 6-month-old female with a vaccination history which included the first dose of meningococcal vaccine (unknown manufacturer and batch number) at two months of age and second dose of meningococcal vaccine (unknown manufacturer and batch number) at four months had never experienced events after vaccine applications. On 21 Sep 2012 the patient's mother was vaccinated with 0.5 ml of Menveo (meningococcal vaccine ACWY conjugated-crm197, batch number: unknown) in the left arm in order to prevent a meningitis outbreak (case: PHHY2012BR083473). The mother breastfed the patient twice daily. That night, after breastfeeding, the patient started to experience vomiting, diarrhea and swollen eyes. "Homemade" oral rehydration was given on 22 Sep 2012. On 23 Sep 2012, the patient vomited five times and had one episode of diarrhea. On 24 Sep 2012, the patient experienced secretion in the eyes. The outcome of the vomitting and diarrhea was reported as worsened. The outcome of the events swollen eyes and secretion in the eyes were not reported. Causality was not reported.

3.5 Gastrointestinal disorders

During this review period, a total of 35 adverse events from 25 case reports were identified under this body system. Of these, two were serious unlisted events (abdominal pain, abdominal pain upper). There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.6 General disorders and administration site conditions

During this review period, a total of 254 adverse events from 106 case reports were identified under this body system. Of these, 14 were serious unlisted events. The serious unlisted events identified were gait disturbance, induration, inflammation, malaise, edema, peripheral edema, vaccination site erythema, vaccination site edema, vaccination site pain and vaccination site swelling. There were no reports of fatal outcomes associated with this body system.

There were three 15-day reports belonging to this SOC and is presented below.

PHHY2012AT081473 / Vaccination site swelling (Spontaneous report/HCP): A female child of unknown age with a medical history of being vaccinated with an unspecified vaccine was vaccinated with Menveo (meningococcal A, C, Y and W vaccine, batch number: X11070 and expiry date: Mar 2013) in the left upper arm on an unspecified date. Within 12 hours after vaccination, the patient experienced redness and swelling at the injection site. The final outcome was reported as complete recovery. The reporter assessed the causality to be suspected to Menveo.

PHHY2012FR078634 / Vaccination site pain (Spontaneous report/HCP): A 19-year-old male with an unspecified medical history was vaccinated with Menveo (meningococcal

groups A, C, W135 and Y conjugate vaccine, batch number: M10145) intramuscularly at an unspecified injection site on 22 Aug 2012. On the same day, the patient was also vaccinated with Repevax vaccine (diphtheria, tetanus, acellular pertussis and poliomyelitis (inactivated) vaccine, batch number: H0046) intramuscularly at unspecified injection site. On 23 Aug 2012, the patient experienced pain at injection site and headache. The patient was supported by the emergency medical service and commissioning unavailable for one day. At the time of report, the patient had recovered without sequelae from pain at injection site and headache. The French health authority assessed the causal relationship between events, Menveo and Repevax as unlikely.

PHHY2012FR090280 / Vaccination site inflammation (Spontaneous report/HCP): A 16-year-old female with an unspecified medical history was vaccinated with a dose of Menveo (meningococcal groups A, C, W135 and Y conjugate vaccine, batch number: M10145) intramuscularly on to right deltoid muscle and with the first dose of Repevax (diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine, batch number: H0046-1) intramuscularly on to right triceps on 13 Sep 2012. Twelve hours later, the patient experienced local reaction with inflammation greater than 5cm and pain. She also experienced headache. The patient was hospitalized and on sick leave for three days. The outcome of the events was not reported. The health authority assessed the causal relationship between the events, Menveo and Repevax as possible.

3.7 Immune system disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This one event was not a serious unlisted event. There were no reports of fatal outcomes associated with this body system.

There was one 15-day report belonging to this SOC and is presented below.

PHHY2012IT076392 / Hypersensitivity (Spontaneous report/HCP): A 17-year-old female with a medical history of multiple allergies and urticarial reaction after intake of niflumic acid was vaccinated with first booster dose of Menveo (meningococcal A, C, Y, W-135 vaccine, batch number: M10105) at a dose of one posologic unit intramuscularly at an unspecified site on 23 Jul 2012. She was concomitantly vaccinated with Epaxal (hepatitis A vaccine, batch number: not reported, other manufacturer) at a dose of one posological unit administered intramuscularly on the same day. On 24 Jul 2012, the patient developed systemic allergic reaction with lip edema, dyspnea and wheals at trunk and limbs. The reaction was treated with cortisonic drug. The final outcome was reported as complete recovery on 01 Aug 2012. The health authority assessed causality as suspected to be related to administration of Menveo.

3.8 Infections and infestations

During this review period, a total of seven adverse events from seven case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were cellulitis, nasopharyngitis, vaccination site cellulitis and vaccination site infection. There were no reports of fatal outcomes associated with this body system.

There were five reports which were 15-day reports belonging to this SOC and are presented below.

PHEH2012US016438 / Nasal pharyngitis (Spontaneous report/HCP): An 11-year-old female with an unknown medical history was vaccinated with Menveo (meningococcal A, C, Y and W-135 vaccine, batch number: M11075) intramuscularly on to left arm on 01 Aug 2012. The patient was concomitantly vaccinated with Adacel (diphtheria, tetanus, acellular pertussis, other manufacturer, batch number: C4247AA,) and Varivax (varicella virus vaccine, other manufacturer, batch number: 0435A2) at a dose of 0.5 ml intramuscularly on 01 Aug 2012. On 03 Aug 2012, the patient experienced swollen, painful, bright red area ('size' of hand) on three-quarters of the arm. On 06 Aug 2012, the patient's mother reported that the patient had onset of dizziness, fever with temperature of 104 degree F, nausea, decreased appetite, disorientation and sore throat with cough on and off for the entire weekend. The area on arm was still slightly red and swollen. The reporter stated that the patient had a remarkable local reaction with arm swelling down to the elbow and was splotchy; fever was also reported during that visit. On 10 Aug 2012, the patient had a return visit for cold and upper respiratory symptoms; the other symptoms had resolved with only a slight residual rash remaining. On an unspecified date, the patient was hospitalized for an unspecified reason and duration. The outcome of the event was reported as complete recovery. The causality was not reported.

PHFR2012GB005179 / Vaccination site infection (Spontaneous report/HCP): A 49-year-old female with an unknown medical history was vaccinated with Menveo (meningococcal A, C, Y and W vaccine, batch number: X10147/ M10147) intramuscularly into the deltoid on 19 Sep 2012. On the same day, the patient's arm swelled and became red. The physician assessed that the patient was infected from the injection and initiated antibiotics. The pharmacist commented that this was more likely to be a local reaction causing pain, resulting in dependent edema in hand. Outcome and causality were not reported.

PHHY2012NO074145 / Erysipelas (Spontaneous report/HCP): This report was erroneously assessed as serious and therefore, downgraded to non-serious on followup. It will not be further discussed.

PHHY2012US067285 / Vaccination site cellulitis (Spontaneous report/HCP): An 11-year-old male with an unknown medical history was vaccinated with Menveo vaccine (meningococcal ACWY vaccine, batch number: M10032) intramuscularly into his left deltoid muscle on 22 May 2012. On the same day, he was also vaccinated with Gardasil vaccine (human papilloma virus vaccine, batch number: 1537AA) intramuscularly into his right arm, and Adacel (diphtheria, tetanus and acellular pertussis vaccine, other manufacturer, batch number: U3486AA) intramuscularly into his left deltoid muscle. On 23 May 2012, the patient developed pain, swelling and erythema of the left deltoid muscle. A diagnosis of cellulitis of left upper arm was made. The patient recovered completely on an unspecified date. Causality was not reported.

PHHY2012US067349 / Cellulitis (Spontaneous report/HCP): A 17-year-old female with an unknown medical history was vaccinated with Menveo (meningococcal A, C, Y and W vaccine, batch number: M10056) subcutaneously into the right arm along with Gardasil (human papilloma virus vaccine, other manufacturer, batch number: 0476AA) intramuscularly into the left arm and with Ipol (poliomyelitis vaccine inactivated, other manufacturer and batch number: H1200) intramuscularly into the left arm on 04 Jun 2012. Within 24 hours after

vaccination, the patient developed erythema and induration which continued to increase in size and cellulitis for which treatment included cefalexin monohydrate. Outcome was reported as condition unchanged as of 06 Jun 2012. Causality was not reported.

3.9 Injury, poisoning and procedural complications

During this review period, a total of 99 adverse events from 95 case reports were identified under this body system. Of these, none were serious unlisted events. There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.10 Investigations

During this review period, a total of eight adverse event from seven case report were identified under this body system. Of these, none were serious unlisted events. There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.11 Metabolism and nutrition disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Neither were serious unlisted events. There was no fatal outcomes associated with this body system or 15-day reports classified under this SOC by leading event.

3.12 Musculoskeletal and connective tissue disorders

During this review period, a total of 27 adverse events from 18 case reports were identified under this body system. Of these, nine were serious unlisted events. The serious unlisted events identified were arthritis, arthralgia, back pain, hemarthrosis, joint stiffness, joint swelling, muscular weakness and pain in extremity. There were no reports of fatal outcomes associated with this body system.

The one 15-day report belonging to this SOC is presented below.

PHHY2012AT098846 / Back pain (Spontaneous report/HCP): An 11-year-old female with a relevant medical history and concurrent conditions of bodily discomfort and pharynx pain was vaccinated with Menveo (meningococcal vaccine, batch number: unknown), unknown dosage, on 10 Oct 2012 in school. When patient returned to her classroom, five minutes later she experienced vertigo and nausea. The patient fainted and was awakened by the teacher. The patient had no memory of this, no reddening of injection site and no swelling. On the same day, the patient also experienced back pain, fever with body temperature 38 degree Celsius, head pain, lightheadedness, nausea, and pain in arm. Menveo was withdrawn. The patient's recovered from the back pain, faint, fever, head pain, light headedness and nausea. The health authority reported the events were suspected to Menveo.

3.13 Nervous system disorders

During this review period, a total of 60 adverse events from 42 case reports were identified under this body system. Of these, five were serious unlisted events. The serious unlisted

events identified were hypoasthesia, paresthesia, peripheral nerve lesion and presyncope. There were no reports of fatal outcomes associated with this body system.

There were six reports which were 15-day reports belonging to this SOC and are presented below.

PHEH2012US016366/ Syncope (Spontaneous report/HCP): A 23-year-old male with an unknown medical history was vaccinated with MenA component of Menveo vaccine (meningococcal A, C, Y and W-135 vaccine, batch number: A11064, expiration date: Dec 2013) reconstituted with sterile water, intramuscularly on 16 Aug 2012. The patient experienced fainting spell after receiving the MenA component of Menveo vaccine reconstituted with sterile water. It was unknown how long the fainting spell lasted. The outcome was reported as unknown. Causality was not reported.

PHEH2012US016367 / Syncope (Spontaneous report/HCP): A female patient of unknown age with an unknown medical history was vaccinated with Menveo (meningococcal A, C, Y, W-135 vaccine, batch number: A11064, Expiry date: Dec 2013) 0.5 ml intramuscularly on an unknown date. The patient experienced syncope episode sometime in 2012 (unspecified date) after receiving Menveo. Outcome and causality were not reported.

PHHY2012DE087243 / Peripheral nerve lesion (Spontaneous report/HCP): A 33-year-old female with a vaccination history which included Mencevax (meningococcal vaccine, other manufacturer, batch number: not reported) on 10 Jun 2009 was vaccinated with Menveo (meningococcal vaccine, batch number: A10137) intramuscularly into the left deltoid muscle on 07 Jun 2012. On 08 Jun 2012, the patient presented with ulnar nerve lesion, pain, weakness, reduced sensibility and paraesthesia in the area of ulnar nerve. On 16 Jun 2012, nerve conduction velocity of ulnar nerve could not be measured. On 28 Jun 2012, nerve conduction velocity of ulnar nerve was delayed. It was reported that, "an infection as reason for ulnar nerve lesion was not very likely and an abscess as reason for ulnar nerve lesion could be ruled out". Outcome was reported as not recovered. The physician assessed these events as suspected to vaccination with Menveo.

PHHY2012FR090277 / Pre-syncope (Spontaneous report/HCP): A 16-year-old male with an unspecified medical history was vaccinated with a dose of intramuscular injection of Menveo (meningococcal groups A, C, W135 and Y conjugate vaccine, batch number: M10145) in the right deltoid muscle on 13 Sep 2012 at 3 pm. On 14 Sep 2012 at 5 am, the patient he experienced fever greater than 38 degree C, headache and lipothymic malaise. The patient was was hospitalized and on sick leave for three days. The outcome of the event was not reported. The health authority assessed the causal relationship between the adverse events and Menveo as unlikely.

PHHY2012FR090294 / Pre-syncope (Spontaneous report/HCP): A 17-year-old male with an unknown medical history was vaccinated with the first dose of Menveo (meningococcal groups A, C, W135 and Y conjugate vaccine, batch number: M10145) intramuscularly on to right deltoid and with Repevax (diphtheria, tetanus, pertussis and polio vaccine, batch number H0046-1) intramuscularly on to right triceps on 13 Sep 2012 at 4:00 pm. On 14 Sep 2012 at 6:15 am, the patient experienced fever with body temperature greater than 38 degree Celsius, headache and lipothymic malaise. The patient was was hospitalized and on sick leave for

three days. The outcome of the events was not reported. The health authority assessed the causal relationship with Menveo and Repavax as unlikely.

PHHY2012SE096074 / Syncope (Spontaneous report/HCP): A healthy 20-year-old female was vaccinated Menveo (meningococcal vaccine, batch number: A11035, expiry date: Jun 2013) on 16 Oct 2012. Twenty-four hours after receiving the Menveo vaccine, the patient experienced dizziness, headache, stiff neck and fainted several times. As of 25 Oct 2012, the patient had undergone unspecified tests in which the results of the test were not provided. The patient had not fainted during the past two days and had no fever or a feeling of sickness . However, dizziness was still present. Causality was not reported.

3.14 Psychiatric disorders

During this review period, a total of six adverse events from three case reports were identified under this body system. Of these, there was one serious unlisted event (disorientation). There were no reports of fatal outcomes.

There was one report which was a 15-day report belonging to this SOC and are presented below.

PHEH2012US016064 / Paranoia (Spontaneous report/HCP): A 23-year-old male with no medical history and concomitant medications was vaccinated with Menveo (meningococcal ACWY vaccine, batch number: X11064) intramuscularly into his deltoid muscle on 14 Aug 2012 at 3:00 pm. On the same day after vaccination at 10:00 pm, the patient experienced paranoia and was anxious, in addition to experiencing bleeding gums after brushing teeth and an inability to sleep through the night. On 15 Aug 2012 at 10:00 pm, the patient had recovered from all the events. Causality was not reported.

3.15 Respiratory, thoracic and mediastinal disorders

During this review period, a total of 11 adverse events from eight case reports were identified under this body system. Of these, two were serious unlisted events (cough, oropharyngeal pain). There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

3.16 Skin and subcutaneous tissue disorders

During this review period, a total of 73 adverse events from 48 case reports were identified under this body system. Of these, six were one serious unlisted events. The serious unlisted events identified were blister, erythema, Henoch-Schonlein purpura, petechiae, purpura and rash. There were no reports of fatal outcomes associated with this body system.

There were two reports which were 15-day reports belonging to this SOC and are presented below.

PHHY2012DE068192 / Henoch-Schoenlein purpura (Spontaneous report/HCP): A 12-year-old male with medical history rhinitis with nose bleed (one week before vaccination with Menveo) was vaccinated with 0.5 ml Menveo (meningococcal A, C, Y and W vaccine, batch number: A11025) intramuscularly on 09 Feb 2012. On 13 Feb 2012, the patient presented with Henoch-Schoenlein purpura. The patient experienced an eruption at lower leg three days after vaccination and strong stomach pain eight days after vaccination. It was reported that ten

days after vaccination while skiing, the patient experienced a hematoma, edema and pain at ankle joints and knees in addition to abdominal pain “sometimes”. The patient was negative for fever, diarrhea, headache or vomiting. Schoenlein purpura was subsequently diagnosed. On physical examination, it was observed that cervical and nuchal lymph nodes were enlarged up to 2 cm and that there was no meningism. The patient was not hospitalized. The outcome was reported as not yet recovered as of 02 Mar 2012. The reporter assessed the causality of the event as suspected to Menveo.

PHHY2012FR071356 / Purpura (Spontaneous report/HCP): A 21-year-old female with a medical history of tobacco use, appendicectomy and amygdalectomy and a vaccination history of Measles-mumps-rubella vaccine in 2001 (without any allergic event), Engerix B vaccine (hepatitis B vaccine) in 2001, Gardasil vaccine (human papillomavirus vaccine) in 2007 and DTP (diphtheria, tetanus and pertussis) vaccine in 2009 was vaccinated with Menveo (meningococcal groups A, C, W135 and Y conjugate vaccine, batch number: M11027, expiration date: Aug 2013) on the afternoon of 13 Aug 2012. Concomitant medications included desogestrel as contraceptive drug. On 14 Aug 2012 at noon, the patient experienced cutaneo-articular edema with purpuric petechial eruption on the internal side of the ankles and one phlyctena on the right Achilles' tendon. Ankles and knees were swollen and stiff; the patient experienced difficulty walking with morning stiffness for approximately one hour. The patient also had bilateral ankle arthritis and was hospitalized on an unknown date. No liquid was found in the joints and pleuropulmonary auscultation was normal. It was reported that the patient “probably” experienced febricula during the night, but no hyperthermia was noted during the hospitalization. Lung X-ray was normal. Hemoglobin was 114 g/L, platelets were 187000, leukocytes were 5460, neutrophils were 3096 and CRP was 18 mg/L expressing mild inflammatory syndrome. Sedimentation was normal at 11 mm after one hour. Blood culture report was pending at the time of this report. Screen for legionnella and pneumococcus antigen and capsid was negative in the urine. The patient was scheduled to be discharged on (b) (6). The final outcome was reported as complete recovery. Causality was not reported.

3.17 Vascular disorders

During this review period, a total of five adverse events from five case reports were identified under this body system. Of these, none were serious unlisted events. There were no reports of fatal outcomes or 15-day reports classified under this SOC by leading event.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA". There was no such case in the reporting period.

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no regulatory actions taken for safety reasons. Changes to the label were not made since the last periodic report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Novartis Vaccines & Diagnostics

Drug Safety and Epidemiology

Periodic Safety Report for the period 19 Nov 2012 – 18 Feb 2013

Menveo® (meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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List of abbreviations

BLA	Biologics License Application
HA	Health Authority
HCP	Healthcare Professional
Non HCP	Non Healthcare Professional

NDA	New Drug Application
NVD	Novartis Vaccines and Diagnostics
SOC	System Organ Class
VAERS	Vaccines Adverse Event Reporting System

1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for Biologics license application (BLA) # 125300 received by Novartis Vaccines & Diagnostics (NVD) and processed by Drug Safety and Epidemiology of Novartis Pharma between 19 Nov 2012 and 18 Feb 2013.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitidis, serogroups A, C, W-135 and Y.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	2	0
Foreign	15	13

- Listings and Vaccines adverse event reporting system (VAERS) forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
6	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
89	0

- Listings and VAERS forms only for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
28	0

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 30 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the reporting period. Of these, 17 were initial reports and 13 were follow-up reports. During this review period, there was one report with a fatal outcome and the report is presented in the respective System organ class (SOC).

During this review period, there were no serious unlisted events reported in the following SOCs:

1. Ear and labyrinth disorders
2. Eye disorders
3. Injury, poisoning and procedural complications
4. Investigations
5. Metabolism and nutrition disorders
6. Pregnancy, puerperium and perinatal conditions

3.1 Blood and lymphatic system disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This event was a serious unlisted event (leukocytosis). There were no fatal outcomes associated with this body system. The report of leukocytosis (PHHY2013GR004625) is described below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2013GR004625 (Spontaneous Healthcare Professional (HCP) report): A 12-year-old male patient with an unspecified medical history was vaccinated with Menveo (meningococcal (serogroups A, C, Y and W-135 vaccine) batch number: not reported). About 10 to 13 days after the vaccination, he experienced headache, vomiting, fever (40 degree Celsius), mild meningeal irritation signs and photophobia. Lab examinations showed mild leukocytosis up to 17.000 (units unspecified) and mild granulocytosis and was negative for infection markers. He received amoxicillin and clavulanate as a precaution. The patient completely recovered 12 hours after the event onset. The physician assessed the events as serious (medically significant). The physician reported the causality as suspected.

3.2 Cardiac disorders

During this review period, a total of one adverse event from one case report was identified under this body system. This event was serious unlisted event (cardio-respiratory arrest) with a fatal outcome. The fatal report of cardio-respiratory arrest (PHHY2012FR105871) is described below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2012FR105871 (Health Authority (HA) report): A 23-year-old male patient with medical history of meningitis, benign measles, acute mild otitis and face cellulitis due to super infection of shaving lesions was vaccinated with first dose of Menveo (batch number:

M10136) intramuscularly. After about five months of vaccination, he was hospitalized for headache with fever and myalgia. At the time of admission, his body temperature was 39 degree C, leukocyte level was 14000, calcitonin prohormone was 4, and other lab tests were reported as normal. White blood cell count was 2800 (units not reported), platelet count was 18000 (units not reported), prothrombin rate was less than 10 percent, activated cephalin time was greater than 180 seconds, fibrinogen level was less than 0.60 g/L, creatinine was 204 mcmol/L, sodium was 131 (units not reported), potassium was 3.3 (units not reported), creatine phosphokinase was 273 (units not reported), calcitonin prohormone was greater than 200 mg/ml, C-reactive protein was 57 mg/L, blood pH was 7.35, pO2 was 69, pCO2 was 19 and lactates was 11 mmol/L. Lumbar puncture was performed and the results were as follows: Cerebrospinal fluid was clear with 3 leukocytes with normal protein concentration. Direct examination was negative. Blood culture was positive for Neisseria meningitides W135. Polymerase chain reaction was done and Neisseria meningitides W135 serogroup was isolated from the liquor. On the same date after about nine hours, he developed purpura on trunk and shoulders associated with worsening of general health status, worsening of myalgia and agitation. He was treated with ceftriaxone sodium. Upon transfer to resuscitation unit, he experienced worsening of consciousness state with tonic-clonic seizure quickly followed by a cardiorespiratory arrest. Following cardiorespiratory arrest, intubation on fiberscopy was performed and cardiopulmonary resuscitation was given for 45 minutes. The patient died on the same day from fulminans purpura secondary to invasive meningococcal infection due to serogroup W135, meningococcemia and cardiovascular arrest. The health authority assessed the causal relationship between meningococcemia and Menveo as unlikely.

3.3 Gastrointestinal disorders

During this review period, a total of ten adverse events from seven case reports were identified under this body system. There was one serious unlisted event (vomiting). The report of vomiting (PHHY2013GR004625) is already presented in section 3.1. There was no fatal outcome associated with this body system. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.4 General disorders and administration site conditions

During this review period, a total of 146 adverse events from 63 case reports were identified under this body system. Of these, 16 were serious unlisted events. The serious unlisted events identified were extensive swelling of vaccinated limb (PHHY2013AR000983), feeling cold (PHFR2012GB005278), feeling hot (PHFR2012GB005278), general physical health deterioration (PHHY2012FR105871), inflammation (PHHY2013AR000974), edema peripheral (PHHY2012US111043), pain (PHFR2012GB005278), performance status decreased (PHHY2012DE115126), pyrexia (PHHY2013AR000983, PHFR2012GB006273, PHHY2012FR105871, PHHY2013GR004625), swelling (PHFR2012GB006273), vaccination site erythema (PHHY2013AR000983, PHHY2013AR000974) and vaccination site swelling (PHHY2013AR000974). The one fatal case of meningococcal meningitis, which also contained the events of general physical health deterioration and pyrexia (PHHY2012FR105871), is presented in section 3.2. The report of pyrexia (PHHY2013GR004625) under this SOC is presented in section 3.1. The remaining 15-day

reports of extensive swelling of vaccinated limb, feeling hot, feeling cold, inflammation, edema peripheral, pain, performance status decreased, pyrexia, swelling, vaccination site erythema and vaccination site swelling belonging to this SOC are presented below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2013AR000983 (Spontaneous Non healthcare Professional (Non HCP report)): A male child under six years of age with a medical history of hemolytic uremic syndrome and diarrhea (at 18 months of age) was vaccinated with Menveo (batch number: M11083,). Next day, the patient experienced erythema and swelling that extended from the zone, back of the shoulder to the hand on the same side of the application. At first, he experienced phlebitis which later developed into to cellulitis. The size of the arm was enlarged 3 times when compared to the normal size. Within 48 hours after vaccination, continued local involvement and loss of function was observed in the patient. The patient was treated with cephalexin, amoxicillin, clavulanate potassium and sulfamethoxazole, trimethoprim and diphenhydramine hydrochloride It was decided to the rotate the antibiotics, amoxicillin-clavulanate and trimethoprim-sulfamethoxazole. The patient also experienced fever on an unknown date. On an unknown date, the child was afebrile with reduced swelling and improved function. Eight days after vaccination, although swelling and erythema had decreased, in the area of the scapula, he presented erythematous papular non-pruritic lesions and petechiae in the armpit region (compromised the entire upper limb and had erythematous papules). The patient complete recovered. The seriousness and causality of the events were not reported.

PHFR2012GB005278 (Spontaneous HCP report): A 47-years-old male patient with unknown medical history was vaccinated with Menveo (batch number: M11007) subcutaneously. On the same day, he experienced cellulitis of the left arm with redness. It was achy; he felt hot and cold and had raised temperature few hours after vaccination. The outcome of the event cellulitis was reported as complete recovery and for other events was not reported. Causality of the event was assessed as suspected.

PHHY2013AR000974 (Spontaneous Non HCP report): A male child patient less than eight years of age with unknown medical history was vaccinated with Menveo (batch number: M11083). Next day, he presented erythema and swelling at the site of application that compromises the shoulder region. He presented with petechiae, inflammation of the left shoulder to the middle of the arm and the area was very red and led to cellulitis. The patient received treatment with cephalexin. After 48 hours of vaccination, the patient continued to present with local involvement and loss of function, so was asked to consult pediatrician who decided to rotate antibiotic, amoxicillin and clavulanate potassium and sulfamethoxazole and trimethoprim. The patient completely recovered. Seriousness and causality of the events was not reported.

PHHY2012US111043 (Spontaneous HCP report): A 12 year old male patient with unknown medical history received vaccination with Menveo (batch number: A11047) and human papilloma vaccine in right arm, hepatitis A vaccine and tetanus diphtheria and acellular pertussis vaccine, into left arm, all on the same day. Two days later, he was diagnosed with fever, headache, body aches, forehead swollen, right arm, forearm and shoulder swollen in the emergency room. The patient was treated with steroids, antibiotics

(unspecified) and diphenhydramine hydrochloride. The patient completely recovered. Seriousness and causality assessment was not reported.

PHHY2012DE115126 (HA report): A 33-year-old male patient's past vaccination history included TBE vaccine, hepatitis A and hepatitis B vaccine, and tick borne encephalitis vaccine. On 20 Sep 2011, he was vaccinated with hepatitis A and hepatitis B vaccine. On 22 Sep 2011, the patient received influenza vaccine and measles, mumps, rubella vaccine. The patient received typhus vaccine on 26 Sep 2011, Rabies vaccine inactivated (batch number: E0896-1,) on 29 Sep 2011, Rabies vaccine inactivated (batch number: E0896-1) on 04 Oct 2011, Menveo batch number: X10137) on 06 Oct 2011 and Rabipur (rabies vaccine, batch number: 4900 11A) on 17 Oct 2011. After vaccinations (latency not specified), the patient presented with depression, discomfort in joints, headache, muscle discomfort, nausea, neurological disorder NOS, tiredness, weakness and had performance status decreased. The outcome was not reported. The case was assessed serious (medically significant). Causal relationship was not reported.

PHFR2012GB006273 (Spontaneous HCP report): A 46-year-old male patient with unknown medical history was vaccinated with Menveo (batch number: M11040) intramuscularly into deltoid of the left arm. Forty eight hours after the vaccination, he experienced severe swelling of left arm and chest wall with fever, sickness and vomiting. The patient received treatment with prednisolone and antibiotics. The patient was suspected to have cellulitis. The patient recovered. The events were reported as serious (medically significant) and suspected by the physician.

One 15 day report with serious listed event associated with this body system is described below.

PHHY2012FR115703 (HA report): A 34 year old male patient with unknown medical history was re-vaccinated with Menveo (batch number: M10145) and typhoid vaccine both on same day. Next day, the patient experienced inflammation at vaccination site (>5cm), induration at vaccination site (>1cm), pain at vaccination site, fever (>38 degree Celsius) and headaches. The patient was supported by the medical emergency unit and was on sick leave for 3 days. The events were unchanged. The events were reported as serious and assessed as possibly related to both the vaccines.

3.5 Immune system disorders

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, none were serious unlisted events. There was no fatal outcome associated with this body system. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

There were two 15 day report belonging to this SOC described below.

PHHY2012AU115038 (HA report): A 33-year-old female patient with unspecified medical history was vaccinated with both Menveo (batch number: not reported) and tetanus, diphtheria and acellular pertussis vaccine on the same day. After vaccination (latency not specified), she developed hypersensitivity reaction. The seriousness and outcome were not reported. Causality was reported as suspected to be related to both vaccinations.

PHHY2012GR106365 (Spontaneous HCP report): A 14 year old male patient with unspecified medical history was vaccinated with Menveo (batch number: unknown). Two days later, he developed pruritus (itch). An unspecified ointment was applied the day after the vaccination but before the rash came out. The physician's final diagnosis was allergic rash. Levocetirizine dihydrochloride was prescribed as a treatment measure. According to the physician, the incident was not significant and no blood examinations were performed since the patient had pruritus in the hands and face. The patient completely recovered. Seriousness was not provided. Causality was reported as not related to Menveo. In this case, the event (Purpura) was captured initially as per the initial information and later removed based on follow up information and was coded to (Allergic rash) and hence this has reflected as "uncoded preferred term" under "uncoded SOC" in the 'Tabulation by Body System of All Events Reported'.

3.6 Infections and infestations

During this review period, a total of eight adverse events from seven case reports were identified under this body system. Of these, six were serious unlisted events. The serious unlisted events identified were cellulitis, meningococcal bacteremia and meningococcal infection. The fatal report of meningococcal bacteremia and meningococcal infection (PHHY2012FR105871) is described in section 3.2 and four reports of cellulitis (PHFR2012GB005278, PHFR2012GB006273, PHHY2013AR000974 and PHHY2013AR000983) are included within this SOC, and are presented in section 3.4. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.7 Musculoskeletal and connective tissue disorders

During this review period, a total of 21 adverse events from 17 case reports were identified under this body system. Of these, six were serious unlisted events. The serious unlisted events identified were back pain (PHHY2012DE118064), flank pain (PHHY2012DE118064), mobility decreased (PHHY2013AR000974, PHHY2013AR000983), musculoskeletal discomfort (PHHY2012DE115126) and myalgia (PHHY2012FR105871). The one fatal report of myalgia (PHHY2012FR105871) is described in section 3.2. The reports of mobility decreased and musculoskeletal discomfort (PHHY2013AR000974, PHHY2013AR000983, PHHY2012DE115126) are presented in section 3.4 and the one report of back pain and flank pain is presented below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2012DE118064 (HA report): A 25-year-old female patient with unknown medical history was vaccinated with Menveo (batch number: A11058) intramuscularly into the left upper arm and with typhoid vaccine, intramuscularly into the right upper arm. On the same day of vaccination, the patient presented with flank pain and back pain lasting, resulting in hospitalization. The patient completely recovered within one day. The causality was not reported.

3.8 Nervous system disorders

During this review period, a total of 29 adverse events from 21 case reports were identified under this body system. Of these, nine were serious unlisted events. The serious unlisted events identified were altered state of consciousness (PHHY2012FR105871), grand mal convulsion (PHHY2012FR105871), headache (PHHY2012FR105871, PHHY2013GR004625), hypotonia (PHHY2012GR113586), meningism (PHHY2013GR004625), nervous system disorder (PHHY2012DE115126), tonic clonic movements (PHHY2012IT116219) and tremor (PHHY2013DE005106). The one fatal report of meningococcal meningitis and presented above in section 3.2, also contained the event terms altered state of consciousness, grand mal convulsion and headache (PHHY2012FR105871) associated with this body system. The one report of meningism and headache (PHHY2013GR004625) is already presented in 3.1 and one report of nervous system disorder (PHHY2012DE115126) is presented in 3.4. The remaining reports are presented below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2012IT116219 (HA report): A 12-year-old male patient was vaccinated with Menveo (batch number: M12014) intramuscularly. The patient was concomitantly treated with cetirizine hydrochloride. Ten minutes after vaccination, the patient experienced vertigo with hyposthenia at lower limbs. After 40 minutes, the patient experienced tonic-clonic contractions of the facial muscles and also the upper limbs muscles and experienced general state of agitation. On the same day, blood pressure was 130/80 mmHg, heart rate was 80 and glycemia was 80 (units and normal range were not reported). The events improved. The events were assessed as serious (medically significant) and causality related to the vaccine.

PHHY2012GR113586 (Spontaneous HCP report): A patient of an unknown age and gender with unspecified medical history was vaccinated with Menveo (batch number: not reported). After receiving vaccination, the patient experienced fever, localized inflammation reaction and muscle hypotonia upper limb at the vaccination site, which resulted in hospitalization. The patient’s condition improved. The causality was not reported.

PHHY2013DE005106 (Spontaneous HCP report): A 46-year-old female patient had a medical history of nocturnal paroxysmal hemoglobinuria. Her past vaccination history included Menveo which was tolerated well. Her concomitant medications included eculizumab. After about two years, she was vaccinated again with Menveo (batch number: A11058) into the left upper arm. On the day of vaccination, she experienced headache, trembling and malaise. The patient was hospitalized after seven days of second vaccination for 2 days. The treating physician confirmed that the symptoms were not caused by an infection. The patient completely recovered. The physician reported the events were serious (medically significant and hospitalization). The causality of the events was not reported.

3.9 Psychiatric disorders

During this review period, a total of six adverse events from five case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were agitation (PHHY2012IT116219, PHHY2012FR105871) and depression (PHHY2012DE115126). The fatal report of agitation (PHHY2012FR105871) associated with this body system is already presented in section 3.2. The 15-day report of agitation

(PHHY2012IT116219) is presented in 3.8 and of depression (PHHY2012DE115126) is presented in 3.4. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

3.10 Respiratory, thoracic and mediastinal disorders

During this review period, a total of five adverse events from two case reports were identified under this body system. Of these, there was one serious unlisted event (epistaxis). The report of epistaxis (PHEH2013US003303) is described below. There was no fatal outcome associated with this body system. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHEH2013US003303 (Spontaneous HCP report): A female patient of unspecified age and medical history was vaccinated with Menveo (batch number: A12002) intramuscularly. On the same day, after vaccination, she experienced feeling of numbness in both arms and legs developed an elevated temperature. Next day, she had fever with a temperature of 98 F at 9 am, 101 F at 11 am and 103.5 F by noon. Her fever maintained with medication for three more days with continuation of numbness in arms and legs. On the same day, she also experienced epistaxis, which she never experienced before, and had blood tinged phlegm (which could be a post nasal drip as per reporter). The outcome, seriousness and causality of the events were not reported.

3.11 Skin and subcutaneous tissue disorders

During this review period, a total of 51 adverse events from 32 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events identified were erythema (PHFR2012GB005278, PHHY2013AR000974), petechiae (PHHY2013AR000974, PHHY2013AR000983), purpura fulminans (PHHY2012FR105871), swelling face (PHHY2012US111043) and vascular purpura (PHHY2013FR002914). The fatal report of purpura fulminans (PHHY2012FR105871) is presented in section 3.2. The reports of erythema, swelling face and petechiae (PHHY2012US111043, PHHY2013AR000974, PHHY2013AR000983, and PHFR2012GB005278) are presented in section 3.4 and the report of vascular purpura is presented below. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

PHHY2013FR002914 (HA report): An 18-year-old female patient with medical history of cystitis and a tobacco use was vaccinated with Menveo (batch number: unknown) intramuscularly along with seasonal influenza vaccine intramuscularly. She was further vaccinated with hepatitis A vaccine intramuscularly after two months. After about one more month, she presented with vascular purpura which began at ankles and spread to the thighs, which resulted in hospitalization for nine days. Despite the unspecified dermocorticoid treatments, no improvement was noted. However, skin biopsy performed showed vasculitis lesions. The patient’s condition was unchanged. Health authority assessed the causal relationship with Menveo and the other suspect drugs as unlikely.

3.12 Vascular disorder

During this review period, a total of two adverse events from two case reports were identified under this body system. Of these, one was serious unlisted event (phlebitis). The report of phlebitis (PHHY2013AR000983) is described in section 3.4. There was no fatal outcome associated with this body system. Please refer to Section 9 VAERS forms and line listings, 'Tabulation by Body System of All Events Reported' for detailed listing of all reported events.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

There was no case in the reporting period where Menveo is listed as a co-suspect medication.

5 Estimate of patient exposure

During this reporting period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period there were no regulatory actions taken for safety reasons. Changes to the label were not made since the last periodic report was submitted.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Novartis Vaccines

Drug Safety and Epidemiology

Periodic Safety Report for the period 19-Feb-2013 – 18-Feb-2014

Menveo® (meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine)

BLA # 125300

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1 Introduction

The Menveo® (meningococcal (serogroups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine) periodic safety report summarizes the post-marketing safety data for Biologics license application (BLA) # 125300 received by Novartis Vaccines (NVx) and processed by Drug Safety and Epidemiology of Novartis Pharma between 19 Feb 2013 and 18 Feb 2014.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by Neisseria meningitides, serogroups A, C, W-135 and Y.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the reporting period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	85	30
Foreign	70	63

- Listings and Vaccine Adverse Event Reporting System (VAERS) forms for all domestic serious/labeled events received during the reporting period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
70	0

- Listings and VAERS forms for all domestic non-serious/unlabeled events received during the reporting period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
469	6

- Listings only for all domestic non-serious/labeled events received during the reporting period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
186	5

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 248 initial and follow-up reports were received from US and non-US sources were submitted to the Agency as 15-day alerts during the reporting period. Of these, 155 were initial reports and 93 were follow-up reports.

During this review period, there were four reports with a fatal outcome and each report is presented in their respective System Organ Class (SOC).

3.1 Blood and lymphatic system disorders

During this review period, a total of 15 adverse events from 12 case reports were identified under this body system. Of these, 10 were serious unlisted events. The serious unlisted events identified were disseminated intravascular coagulation, granulocytosis, hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, leukocytosis, lymphadenitis, lymphadenopathy, and spleen disorder. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHFR2013GB001171 (Spontaneous report (SR)/Health Care Professional (HCP)): A 33-year-old male subject was vaccinated with Menveo. During the next year he was diagnosed with **hemolytic uremic syndrome**. He received an extra dose of Menveo 15 months after first dose. The subject was fine at the time of reporting.

PHHY2013AR012968 (SR/HCP): A subject with no remarkable medical history was vaccinated with Menveo. After an unspecified time, the subject had an upper respiratory infection. Later, the subject had a bruise on buttocks and mild unspecified trauma. Three days later, the subject fell from the stairs and presented with scalp injury. On exam, the subject was noted to have petechiae on the lower extremities. The subject underwent hemogram and coagulogram which revealed low platelet count (>10000 unspecified units). The subject was diagnosed with **idiopathic thrombocytopenic purpura** (ITP) and hospitalized. The subject was treated with two doses of gamma-globulin (immunoglobulin g human). The physician stated it was not related to the vaccine, because the subject presented a diagnosis of infection in the upper respiratory tract infection, and thus viral infection may be the possible triggering factor. The subject completely recovered and not presented with new episodes of ITP.

PHHY2013FR080226 (SR/HCP/Health Authority (HA)): A 36-year-old female subject was vaccinated with booster dose of Menveo. One day after vaccination, she experienced a reaction at the injection site (inflammation greater than 5 cm, pain, and induration), **lymphadenitis (**anatomic location not reported**),** and fever over than 38 degrees Celsius. She consulted in the emergency unit; it was not reported whether any treatment was provided. The subject was noted to experience “incapacity” for one day and was noted to be recovered in six days. It was concluded that, these symptoms were related to Menveo vaccination.

PHHY2013FR083362 (SR/HCP/HA): A 29-year-old female subject was vaccinated with booster dose of Menveo. On the same day, approximately four hours post vaccination, the subject experienced vaccination site reaction (pain, inflammation, and induration),

lymphadenitis with paresthesia of upper limb, pyrexia (more than 38 degree C) and headache. Three days after beginning of the events, the subject had not recovered. According to the physician, there was no other explanation than the vaccination in the occurrence of these adverse events. Health authority suspected a causal relationship between the events and suspect vaccine.

PHHY2013US044794 (SR/HCP/HA): A 26-year-old female subject with a history of "too many platelets" was vaccinated with Menveo into the left deltoid region of arm. One day after vaccination, she had a "red raised reaction which was in a size of quarter". On an unknown date, she underwent a lab test (not specified) "**to have spleen removed**" and no other information was provided regarding this condition. The outcome of the events was reported as completely recovered.

3.2 Cardiac disorders

During this review period, a total of 13 adverse events from 12 case reports were identified under this body system. Of these, 12 were serious unlisted events. The serious unlisted events identified were bradycardia, bundle branch block right, cardiac arrest, cardio-respiratory arrest, coronary artery dilatation, cyanosis, palpitations, supraventricular tachycardia, and tachycardia. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There was one reported fatal outcome associated with this body system (PHHO2010US12589).

PHHO2010US12589 (Clinical Trial (CT)-HCP): A 16-month-old male infant was vaccinated with four doses of Men ACYW conjugate study vaccine. Approximately five months after the last dose, the subject presented to the emergency department (ED) for possible seizure, unspecified congestion, and fever. It was noted that the subject experienced "eyes rolled up in his head", foaming at the mouth, and generalized tonic-clonic movements which lasted 30 seconds to one minute. The subject was diagnosed with upper respiratory tract infection and fever. Five days later, the subject experienced a sudden syncopal episode, **cardiac arrest,** and acute epistaxis; the subject died. Autopsy examinations revealed focal deep scalp hemorrhage, left temporal lobe arachnoid cysts, laryngeotracheobronchitis, and follicular hyperplasia of lymph nodes, Peyer's patches, and splenic white pulp. The investigator concluded that based on the scene circumstances and autopsy findings, as well as review of medical records and law enforcement investigation, the cause of death was undetermined. The investigator did not suspect a causal relationship between the events and vaccine.

PHHY2013CH111645 (SR-HCP): A male subject of unspecified age with no underlying diseases or allergic reactions to food was vaccinated with Menveo. Seventeen hours after vaccination, he experienced hypotension, **bradycardia**, and chills. His arterial blood pressure was 80/50, pulse was 41/min, and respiratory frequency was 8/min. The events subsided after three hours. The causality was assessed as suspected to the vaccination with Menveo.

PHHY2013GR099839 (SR-HCP): An 11.5-year-old child of unspecified gender was vaccinated with Menveo. Five-to-ten minutes after vaccination, the child became pale and returned to the clinic with complaints of not feeling well; the child fainted. It was noted that the child’s fingers became blue and that his pulse was 40 (beats per minute). It was reported

that the child experienced hypotension, and “arrhythmia and more specifically **bradycardia”**. The child did not recover and was hospitalized.. The physician reported that the child also experienced intense swelling at the vaccination site which appeared red and warm which was the “size of a lemon”. The child was discharged from the hospital in a good condition.

PHHY2013GR110005 (SR-HCP): A 14-year-old female subject with no history of allergic reaction to food, drugs or vaccines was vaccinated with Menveo. Four days after vaccination, she experienced one episode of **supraventricular tachycardia** with a pulse rate of 200 and visited a cardiologist (reporter) one hour after experiencing the event. Complete blood count, ECG (electrocardiogram), and Holter 24 hour monitor were reported to be normal. Final diagnosis was supraventricular tachycardia. The event outcome was completely recovered. The event was reported as suspected to Menveo.

PHHY2013IT027391 (SR-HCP): A 13-year-old male subject with a past history of unspecified surgery and disease of central nervous system and current condition of tetraplegia with C5-C6 injury was vaccinated with the first booster dose of Menveo and diphtheria, tetanus and pertussis vaccine. On the same date, in the afternoon, the subject visited his family doctor due to generalized malaise; paracetamol was administered. Two days later (post vaccination Day #2), the subject presented again with cough and catarrh and underwent unspecified diagnostic testing (results not provided). On the following day (post vaccination Day #3), the subject experienced unspecified “breathing problems”. Upon arrival of the ambulance, the subject experienced **cardiorespiratory arrest;** he was subsequently hospitalized. He was intubated, resuscitated and ventilated with non-self-inflating bag. He was discharged on the same day. The events were suspected to be related to the vaccine.

PHHY2013US069511 (SR-HCP): An 11-year-old male subject was vaccinated with Menveo, human papilloma virus vaccine, and tetanus, diphtheria and acellular pertussis vaccine in the same arm. He experienced a fainting episode within five minutes after injection. He became pale and developed hypotension. He also presented with sweating and weakness. Electrocardiogram performed showed an incomplete **right bundle branch block**. Outcome of the events was reported as complete recovery.

PHHY2013US097170 (SR-HCP): A 17-year-old poly-medicated female subject with a medical history of hypothyroidism, bipolar disorder, GERD (gastroesophageal reflux disease), anaphylaxis, hyperlipidemia, environmental allergies, constipation, asthma - mild intermittent, depression, and smoking was vaccinated with Menveo. Approximately seven minutes after vaccination she started to complain of tightness in her throat and mild difficulty swallowing. She was given diphenhydramine hydrochloride and monitored for another 30 minutes. She was feeling better and her symptoms were gone. She was sent to home. During night she woke up feeling dizzy, weak and tightness in her throat. She was given a loratadine and was sent back to sleep. She woke next morning and ate a normal breakfast but continued to have dizziness, weakness, and tightness in throat. It became worse around afternoon and she was taken to an urgent care. After reaching, she continued to complain of dizziness, weakness, and difficulty swallowing. An EKG showed that she had **tachycardia**. She was sent to the hospital for suspected allergic reaction to vaccine. She was given an intravenous bolus of saline, meclozine hydrochloride, nicotinic acid, and ketorolac tromethamine. She felt better after the treatment.

PHHY2013US110736 (SR-HCP): A 27-year-old female subject was vaccinated with Menveo in the left arm. On the same day, she experienced rash and hives on the left arm and left posterior thigh within hours of receiving vaccine. Further on she also experienced intermittent dizziness, moderate to severe headache, blurry vision, shortness of breath and **palpitations**. Following these events, she had to visit the ER. Final outcome of the events was condition unchanged.

3.3 Ear and labyrinth disorders

During this review period, a total of seven adverse events from six case reports were identified under this body system. Of these, one was serious unlisted event. The serious unlisted event identified was vertigo. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2013FR014768 (SR-HCP (HA)): A 31-year-old female subject with a medical history of parathyroid disorder (not specified) which was treated with ciprofloxacin was vaccinated with Menveo along with typhoid vaccine. Five days after vaccination she experienced left-sided sudden **deafness** associated with tinnitus for approximately one hour. On the following day, (approximately two hours after the stop of tinnitus), she experienced dizzy spells with nausea but without vomiting. On the same day, she was hospitalized and ENT (Ear-Nose-Throat) examination was performed, which showed left cophosis and instability feeling during movements. She had no spontaneous nystagmus but had mild left head-shaking nystagmus. She also had virological work up on the same day of hospitalization, which showed Cytomegalovirus and Epstein Barr virus primary infection. She received corticosteroid, calcium carbonate and valaciclovir as a treatment for the events. Six days later, she was discharged from the hospital without clear improvement. Health Authority assessed the causal relationship with Menveo and typhoid vaccine as unlikely. The outcome of the events was not reported.

3.4 Eye disorders

During this review period, a total of 35 adverse events from 29 case reports were identified under this body system. Of these, 15 were serious unlisted events. The serious unlisted events identified were blepharospasm, conjunctivitis, eye movement disorder, mydriasis, photophobia, and vision blurred. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2013AT027901 (SR-HCP (HA)): A 14-year-old male subject was vaccinated with Menveo. One day after vaccination he experienced vaccination site pain and swelling, vomiting, lightheadedness, nausea, fever, **light sensitivity to eye** and throbbing headache. The outcome of the events was improving. The reporter assessed the events as medically significant and suspected to be related to Menveo.

PHHY2013IT074736 (SR-HCP (HA)): A female subject of unknown age was vaccinated with the booster dose of Menveo. On the same day she experienced high fever (39.8 degree Celsius), edema and redness at injection site, headache, **photophobia**, abnormal dreams and loss of appetite. She recovered completely. The reporter assessed the events as serious and suspected to be related to Menveo.

PHHY2013US140366 (SR-HCP (HA)): An 11-year-old female subject was vaccinated with Menveo intramuscularly into right arm. On the same day, she also received human papilloma virus vaccine intramuscularly into left arm and tetanus/diphtheria/acellular pertussis vaccine intramuscularly into right arm. On the same day, five minutes after vaccinations, she was noticed by medical assistant falling off the table with **eyes rolled**, shaking and there was incontinence of urine. She was taken to hospital (emergency visit) by ambulance. Outcome of the events was reported as recovered.

3.5 Gastrointestinal disorders

During this review period, a total of 95 adverse events from 72 case reports were identified under this body system. Of these, 17 were serious unlisted events. The serious unlisted events identified were abdominal pain, abdominal pain upper, acute abdomen, cheilitis, diarrhea, dysphagia, glossodynia, mouth hemorrhage, nausea, oral disorder, strawberry tongue, and vomiting. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHEH2013US008408 (SR-HCP (HA)): A 30-year-old poly-medicated female subject who was allergic to latex and promethazine was vaccinated with Menveo intramuscularly in the right deltoid. On the same date, she experienced sudden severe stomach pain and nausea, exhaustion, dizziness and dry heaving. Two hours later, she experienced severe vomiting and diarrhea. Four hours later, she visited ER with an uncontrollable **vomiting** and severe nausea. She was examined for stomach illness. She was given 2 bags of saline (intravenous sodium chloride), ondansetron hydrochloride, pantoprazole sodium sesquihydrate, ranitidine, diphenhydramine, prochlorperazine edisylate, IV contrast, chlorpromazine hydrochloride, diazepam, and methylprednisolone sodium succinate. The events vomiting and dry heaving stopped after taking diazepam. When diazepam was stopped, nausea and vomiting returned requiring overnight admission with intravenous hydration. At the time of discharge, she was diagnosed with nausea, vomiting and an adverse reaction to meningococcal vaccine. She was given prescription for diazepam for the next three days. The outcome of the events was reported as recovered. The events nausea and vomiting were assessed as serious (medically significant and hospitalization).

PHHY2012US098877 (SR-HCP (HA)): A 12-years-old female subject was vaccinated with Menveo diphtheria, tetanus and acellular pertussis vaccine and human papilloma vaccine and varicella virus vaccine. Approximately 20 minutes after vaccination, she began to have **burning of tongue** which progressed to swelling of lips and eyelids with flushing chest up. Her blood pressure was stable. Pulse oximetry was 94 %; she was given epinephrine twice and methylprednisolone acetate which led to improvement in her condition. She made a visit

to the ER and was admitted into a hospital. The final outcome of the reaction was reported as not yet recovered.

PHHY2013AR026490 (SR/Non-HCP): A subject of unspecified age and gender was vaccinated with Menveo. One day after vaccination, the subject developed intense abdominal pain that limited ambulation and was hospitalized. The subject was diagnosed with **acute abdomen**. The cause was suspected to be appendicitis or peritonitis. The subject recovered completely.

PHHY2013FR080255 (SR-HCP (HA): A 24-year-old male subject was vaccinated with booster doses of Menveo, inactivated influenza virus vaccine and typhoid vaccine. On the same day he was vaccinated with the first dose of measles, mumps and rubella vaccine. On the same date, four hours after vaccinations he presented with fever (more than 38 degrees C), headache and **vomiting**. He was admitted in emergency care unit. According to the physician, there were no other explanations than the vaccinations in the occurrence of these adverse events. The events were assessed as medically significant.

3.6 General disorders and administration site conditions

During this review period, a total of 817 adverse events from 363 case reports were identified under this body system. Of these, 82 were serious unlisted events. The serious unlisted events identified were asthenia, chills, extensive swelling of vaccinated limb, feeling abnormal, feeling hot, foaming at mouth, gait disturbance, general physical health deterioration, general symptom, hyperpyrexia, induration, inflammation, irritability, malaise, necrosis, oedema, oedema peripheral, pain, pyrexia, swelling, tenderness, vaccination site erythema, vaccination site induration, vaccination site pain, vaccination site pruritus, vaccination site rash, vaccination site swelling, vaccination site urticaria, and vaccination site warmth. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

Table 3-1 15-Day alerts from the General disorders and administration site conditions SOC

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
PHEH2013US012000/SR-HCP	12/M	Vaccination site induration/vaccination site erythema/vaccination site warmth/vaccination site pruritus/vaccination site edema/incorrect route of drug administration	Menveo	Tetanus, diphtheria, and pertussis vaccine	NA	NA	Menveo was given subcutaneously (incorrect route) in the right arm and Boostrix in the left arm. Same day after vaccination, the subject experienced itching, warmth, erythema, and edematous reactions around injection site. The next day he experienced redness and induration in right arm and was hospitalized. Subject recovered after two to three days.
PHEH2013US017567/SR-HCP	18/M	Fatigue/headache/pyrexia /chills/vaccination site pain/inappropriate schedule of drug administration/incorrect route of drug administration	Menveo	NA	NA	NA	The subject was vaccinated with first dose of Menveo subcutaneously (wrong route) and was again vaccinated with Menveo intramuscularly. Next day the subject experienced headache, fever, chills, fatigue, and soreness at the administration site and visited emergency room. The subject recovered seven days later. The events were reported as medically significant.
PHEH2013US022645/SR-HCP	12/M	Vaccination site erythema/vaccination site urticaria/vaccination site rash/vaccination site warmth/vaccination site induration	Menveo	NA	Eczema/lactase deficiency	NA	Twenty one hours after vaccination, he had 20x10 cm irregular-bordered, ovoid, large raised confluent erythematous hot urticarial patch with well demarcated border covering the right upper outer arm. The area was warm and indurated. The subject was treated with diphenhydramine, ranitidine and ice and the symptoms improved. The events were non-serious.
PHFR201	52/F	Local swelling/pain in	Menveo	NA	NA	NA	Unspecified time after vaccination, the

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
3GB000944/SR-HCP		extremity/erythema					subject experienced extremely swollen arm, very large size and severely sore arm. She received two courses of antibiotics. The arm was very red. The outcome was improving. The events were assessed as serious and as related to the vaccination.
PHHO2009TW16207/CT-HCP	9 weeks/F	Pyrexia	Menveo	NA	Asplenia (without cardiac abnormality)	Pneumococcal vaccine/inactivated polio vaccine/haemophilus influenza B vaccine/diphtheria, tetanus and polio vaccine/penicillin V	One day after vaccination the subject experienced fever which resulted in hospitalization. The subject was treated with ampicillin and gentamicin and she recovered within two days. The event was suspected to be related to vaccine.
PHHY2013AR000983/SR-HCP	6/M	Face edema/cellulitis/mobility decreased/pyrexia/extensive swelling of vaccinated limb/vaccination site erythema/petechiae/rash erythematous/rash popular	Menveo	NA	Hemolytic uremic syndrome/ diarrhea	NA	One day after vaccination the subject experienced erythema and swelling that extended from the zone, back of the shoulder to the hand on the same side of application. He experienced cellulitis. The subject was treated with cephalexin, amoxicillin/clavulanate, and sulfamethoxazole/trimethoprim. Within 48 hours loss of function of hand was observed. He also had fever. He received diphenhydramine. Eight days after vaccination, the subject experienced

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
							erythematous non-pruritic lesions and petechiae in the armpit. Later whole upper limb was compromised. The subject recovered after antibiotic treatment.
PHHY2013AR135076/SR-HCP	Unk/M	Extensive swelling of vaccinated limb/vaccination site induration/vaccination site erythema/vaccination site warmth/injected limb mobility decreased	Menveo	NA	NA	NA	Twelve hours after vaccination, the child experienced major erythema and increase of temperature at the application site, extending from the shoulder to elbow. Twenty four hours later, he experienced major tumefaction up to twice the diameter of the arm and had functional impotence. He also experienced induration of the upper limb. Two days after vaccination he was prescribed antihistamines as treatment. The subject recovered on the fifth day of the treatment.
PHHY2013AT060575/SR-HCP	Unk/M	Pyrexia/headache	Menveo	NA	NA	NA	Twelve hours after vaccination the subject experienced fever of 39.5 C and headache. The subject recovered from the events. The events were assessed as medically significant.
PHHY2013CZ070994/SR-HCP	4/M	Extensive swelling of vaccinated limb/vaccination site erythema/vaccination site warmth/vaccination site pain/chills	Menveo	NA	NA	NA	Same day after vaccination, the subject had increase in the volume of the upper (vaccinated) arm with redness, heat, pain without fever. He also experienced chills. The subject received unspecified treatment and recovered completely from the events. The extensive edema and erythema were considered as serious and related to the vaccination.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
PHHY2013CZ149344/SR-HCP	36/M	Vaccination site edema/vaccination site rash/rash maculo-papular/vaccination site pruritus	Menveo	NA	HIV infection/hemorrhoids	Hesperidin/diosmin	Approximately seven days after vaccination, the subject experienced massive and prolonged edema and exanthema at vaccination site which measured up to 10 to 15 cm in diameter along with maculopapulose red exanthema and pruritus around injection site. Bisulpen hydrochloride was given as treatment. The events were still ongoing. The events were assessed as serious and as related to Menveo.
PHHY2013FR067477/SR-HCP	35/F	Injection site reaction/injection site inflammation/injection site pain/injection site induration/headache	Menveo	Influenza vaccine/typhoid vaccine	NA	NA	One day after vaccination, the subject experienced injection site reaction with inflammation, pain, and induration in a area of 5cm and headache. She recovered within eight days. The events were assessed as medically significant. The causality was reported as possible.
PHHY2013FR067482/SR-HCP	24/M	Chills/injection site pain	Menveo	Influenza vaccine/yellow fever vaccine/typhoid vaccine	NA	NA	One day after vaccination the subject experienced chills and injection site pain. The outcome was unknown. The events were assessed as medically significant. The causality was reported as unlikely.
PHHY2013FR067501/SR-HCP	25/M	Pyrexia/headache/myalgia/injection site pain	Menveo	Typhoid vaccine/influenza vaccine	NA	NA	Four hours after vaccination, the subject experienced fever (more than 38 degree C), headache, myalgia, and pain at injection site. The subject recovered three days later. The events were assessed as medically significant and as related to vaccinations.
PHHY201	18/M	Pyrexia/headache/nause	Menveo	Typhoid	NA	NA	Four days after vaccination, the subject

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
3FR083284/SR-HCP		a		vaccine/influenza vaccine			experienced fever (over 38 degree C), headache, nausea, and asthenia. The subject recovered after three days. The events were reported as medically significant and as unlikely related to the vaccinations.
PHHY2013FR083298/SR-HCP (HA)	Unk/M	Asthenia/headache/myalgia/vaccination site pain	Menveo	Typhoid vaccine	NA	NA	Same day after vaccination, the subject experienced injection site pain, headache, myalgia, and asthenia. The subject recovered after four days. The events were assessed as medically significant and as possibly related to vaccinations.
PHHY2013FR086097/SR-HCP (HA)	60/F	Pyrexia/vaccination site reaction/vaccination site erythema/vaccination site edema/headache/vomiting	Menveo	NA	Hypothyroidism/hypertension/herpes zoster/migraine	Valsartan, hydrochlorothiazide/zolmitriptan/omeprazole/levothyroxine sodium	Five days after vaccination, the subject experienced local reaction with erythematous edema, marked pain on vaccinated arm, fever (until 39 degree C), vomiting, and headache. The subject was treated with antibiotics. Fever regressed in two-three days and local reaction regressed in 21 days. The health authority assessed events as serious and as related to Menveo.
PHHY2013FR091891/SR-HCP (HA)	58/M	Drug ineffective	Menveo	Prednisone/tacrolimus/mycophenolate mofetil	Hypertension/liver transplant	NA	Menveo was given to immunosuppressed subject. There was no sero-conversion after the immunization with Menveo. The vaccination was reported to be ineffective. The health authority assessed as the event as medically significant and suspected a drug interaction between tacrolimus, mycophenolate mofetil, and prednisone.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
PHHY2013FR091902/SR-HCP (HA)	56/M	Drug ineffective	Menveo	Ciclosporin/prednisone	Hepatocellular carcinoma (due to hepatitis C)/liver transplant	NA	Serotypes were performed before and after the vaccination for serogroups A, C, Y, and W-135. The subject had not yet presented immunity against serogroups A, Y and W135. There was no sero-conversion after the two injections of Menveo. The event was assessed as medically significant and health authority reported a possible drug interaction between ciclosporin, and prednisone.
PHHY2013FR091946/SR-HCP (HA)	56/F	Drug ineffective	Menveo	Mycophenolate mofetil/prednisone/tacrolimus	Liver transplant/ poikilocytosis/renal transplant	NA	The subject was vaccinated with Menveo subcutaneously twice. The subject had presented immunity against serogroups W135 and Y. There was no sero-conversion for sero-group A after two injections. Health authority assessed the event as medically significant and suspected a drug interaction between tacrolimus, mycophenolate mofetil and prednisone.
PHHY2013FR091954/SR-HCP (HA)	41/F	Drug ineffective	Menveo	Tacrolimus/prednisone/azathioprine	Poikilocytosis/renal transplant	NA	The subject was subcutaneously vaccinated with Menveo. The subject only had sero-conversion for sero-group C. The health authority assessed the event as medically significant and suspected a drug interaction between tacrolimus, azathioprine, and prednisone
PHHY2013FR091955/SR-HCP (HA)	61/M	Drug ineffective	Menveo	Sirolimus/prednisone/mycophenolate mofetil	Renal transplant/ hypertension	NA	The subject was vaccinated with two doses of Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject only presented with sero-conversion for sero group C. The health authority

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
							suspected possible interaction between sirolimus, prednisone, and mycophenolate mofetil.
PHHY2013FR091966/SR-HCP (HA)	41/M	Drug ineffective	Menveo	Tacrolimus/prednisone/everolimus	Liver transplant/ hepatitis B virus test positive/hepatic cirrhosis	NA	The subject was vaccinated with two doses of Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject only presented with sero-conversion for sero group W-135. The health authority suspected possible interaction between tacrolimus, prednisone, and everolimus.
PHHY2013FR091968/SR-HCP (HA)	65/M	Drug ineffective	Menveo	Mycophenolate mofetil/ciclosporin	Hepatocellular carcinoma /liver transplant/ hepatitis C virus test positive	NA	The subject was vaccinated with Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject only presented with sero-conversion for sero groups C and W-135. The health authority suspected possible interaction between mycophenolate mofetil and ciclosporin.
PHHY2013FR091971/SR-HCP (HA)	56/M	Drug ineffective	Menveo	Prednisone/tacrolimus/mycophenolate mofetil	Hepatocellular carcinoma /liver transplant/ hepatitis B virus test positive	NA	The subject was vaccinated with Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject only presented with sero-conversion for sero groups A, Y, and W-135. There was no sero-conversion for sero group C. The health authority suspected possible interaction between tacrolimus, prednisone, and mycophenolate mofetil.
PHHY2013FR091981/SR-HCP	40/M	Drug ineffective	Menveo	Prednisone/azathioprine/tacrolimus	Renal failure chronic/hy	NA	The subject was vaccinated with Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
(HA)					pertension /renal transplant		only presented with sero-conversion for sero group Y. The health authority suspected possible interaction between tacrolimus, azathioprine, and prednisone.
PHHY2013FR091991/SR-HCP (HA)	44/M	Drug ineffective	Menveo	Prednisone/tacrolimus/mycophenolate mofetil/meningococcal vaccine	Hepatitis B/hepatocellular carcinoma /liver transplant	NA	The subject was vaccinated with Menveo and another meningococcal A, C, Y, W-135 vaccine subcutaneously. Serotypes were performed before and after vaccination. There was no sero-conversion after the vaccinations. The health authority suspected possible interaction between tacrolimus, mycophenolate mofetil, and prednisone.
PHHY2013FR092025/SR-HCP (HA)	54/M	Drug ineffective	Menveo	Tacrolimus/prednisone	Hepatitis B virus test positive/liver transplant/ hepatocellular carcinoma	NA	The subject was vaccinated with two doses of Menveo subcutaneously. Serotypes were performed before and after vaccination. The subject only presented with sero-conversion for sero group Y and presented immunization only against sero-group C. The health authority suspected possible interaction between tacrolimus and prednisone.
PHHY2013IT034657/SR-HCP	13/F	Induration/pain in extremity/erythema/vaccination site swelling/vaccination site erythema/vaccination site pain	Menveo	NA	NA	NA	Same day after vaccination, the subject experienced redness, pain and swelling at the injection site. The day after the reactions worsened in terms of extension and the general practitioner suggested taking cortisone. The next day, the subject experienced edema, pain and erythema in upper limb. The subject was treated with antihistamine drug and she improved.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
PHHY2013KR043311/SR-Non HCP	4/F	Extensive swelling of vaccinated limb/erythema	Menveo	NA	Rhinitis	NA	Same day after vaccination, the subject experienced arm edema and redness. The arm oedema worsened and her upper arm was swollen and red. The outcome of the events was ongoing.
PHHY2013KR130323/SR-HCP	12/M	Extensive swelling of vaccinated limb/wrong technique in drug usage process	Menveo	NA	NA	NA	The subject was vaccinated with Menveo with already used needle (used for another vaccination). He experienced severe swelling of whole arm including upper limb which persisted for two days and later recovered after using antibiotics.
PHHY2013US069319/SR-Non HCP (HA)	11/M	Gait disturbance/swelling/local swelling/pain in extremity/hepatic enzyme increased	Menveo	Diphtheria, pertussis, and tetanus vaccine/varicella virus vaccine	Viral infection	NA	The subject was vaccinated with Menveo in the left arm, and the other two vaccinations in the right arm on the same day. Four days after vaccinations, he experienced pain and swelling in hands and feet. It later spread to the whole body. He could barely walk and attend school. He also had elevated liver enzymes. The events were assessed as serious causing disability.
PHHY2013US110851/SR-HCP (HA)	16/F	Feeling abnormal/face edema/pharyngeal edema/oropharyngeal pain/blood creatine increased	Menveo	Polio vaccine/human papilloma vaccine	Renal transplant/ food allergy	Clindamycin /prednisone/ colecalciferol/azathioprine/sodium bicarbonate/ tacrolimus/calcium carbonate	The subject was vaccinated with Menveo and polio vaccine in the left arm and human papilloma vaccine in the right arm. The next day she felt weird and presented to emergency room (ER). Her throat was hurting, and it felt swollen. She also had facial edema. She was treated with diphenhydramine hydrochloride, famotidine, methylprednisolone, ipratropium bromide and salbutamol, and epinephrine and

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine /Drugs	Relevant history	Concomitant medications	Description
							recovered.
PHHY2014FR011152/SR-HCP (HA)	3/M	Local reaction	Menveo	NA	Sickle cell anaemia/hypersplenism/transfusion	Deferasirox/folic acid	Same day after vaccination, he was sub febrile. Two days after vaccination, he visited emergency room due to swelling, heat, redness from forearm to the bend of the elbow with flexion difficulties. He was diagnosed with vaccine allergy and was treated with mequitazine and alcoholized dressing. He recovered completely.

*SR=Spontaneous report, HCP=Health care professional, M=Male, F=Female, HA=Health Authority, NA=Not Applicable

3.7 Immune system disorders

During this review period, a total of 17 adverse events from 15 case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted event identified was serum sickness. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2013AR073465 (SR-HCP): A 2-year-old male subject was vaccinated with Menveo. Twenty four hours after vaccination, he experienced fever of 38 degree C, erythema and edema in the application site. Thirty six hours after vaccination, he had no fever. Forty eight hours after vaccination, he developed a lesion which extended involving the entire right arm. He was prescribed antibiotic (cefalexine) and anti-histamine (hidroxine). He continued with these treatments and the condition improved. He was diagnosed with **localized allergic reaction**. Swelling, edema and erythema had been resolved, but he had some excoriations from scratching in the lower limb. The causality was reported as suspected to be related to Menveo.

PHHY2013GR104691 (SR-HCP): A 15-year-old male subject with no medical history of allergies with food or medicinal products was vaccinated with Menveo. Fifteen minutes after the vaccination, he experienced numbness at his upper limb, angioedema at his lips and face, his face had a blue color and he had a difficulty in swallowing. He was taken to the hospital where he was treated with methylprednisolone IV and cetirizine hydrochloride. The physician diagnosed **allergic reaction** to Menveo. He recovered completely after two hours. Physician assessed the events as medically significant and as suspected to Menveo.

PHHY2013PL053744 (SR-HCP (HA)): An adult subject of unspecified age and gender was vaccinated with Menveo and hepatitis A vaccine. Ten minutes after vaccinations, subject experienced an **allergic reaction** including paleness, loss of consciousness and first episode of seizures. After one and a half minute, consciousness returned. The event was described as a hypotonic-hyporeactive episode with apnea and seizure. The examinations did not reveal any signs of deficits. There were no symptoms of damage to the central nervous system. The outcome of event was not reported. The event was reported as serious (medically significant) and as related to Menveo.

PHHY2013US056701 (SR-HCP (HA)): An 11-year-old male subject was vaccinated with Menveo, human papilloma virus vaccine and diphtheria, tetanus and acellular pertussis vaccine. Two days later, he developed **serum reaction** to vaccination. The event outcome was reported as condition unchanged

PHHY2014US001132 (SR-HCP (HA)): An 18-year-old female subject was vaccinated with Menveo and human papilloma virus vaccine. Two days after vaccination, she developed **serum reaction**. The outcome of event was reported as condition unchanged.

3.8 Infections and infestations

During this review period, a total of 53 adverse events from 47 case reports were identified under this body system. Of these, 43 were serious unlisted events. The serious unlisted events identified were cellulitis, dermo-hypodermitis, groin abscess, lymph node abscess, meningitis, meningitis aseptic, meningitis bacterial, meningitis viral, meningococcal bacteremia, meningococcal infection, meningococcal sepsis, nasopharyngitis, orchitis, skin infection, soft tissue infection, tonsillitis, upper respiratory tract infection, vaccination site cellulitis, vaccination site infection, and viral diarrhea. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were 3 reported fatal outcomes associated with this body system (PHHY2012FR105871, PHHY2013US033977, and PHHY2013US116861).

PHHY2012FR105871 (SR-HCP (HA)): A 23-year-old male subject with medical history of meningitis, benign measles, acute mild otitis and face cellulitis due to super infection of shaving lesions was vaccinated with first dose of Menveo. Approximately five months after vaccination he consulted at emergency unit for headache with fever and myalgia. At the time of admission, his body temperature was 39 degree Celsius. Later polymerized chain reaction (PCR) was done and the Neisseria meningitidis isolated from the liquor was a W135 serogroup. On the same date, he developed purpura on trunk and shoulders associated with worsening of general health status, worsening of myalgia and agitation. As a corrective action he was administered with ceftriaxone sodium. He was transferred to resuscitation unit. Immediately after the transfer he experienced worsening of consciousness state with tonic-clonic seizure which was quickly followed by a cardiorespiratory arrest. Following cardiorespiratory arrest, intubation on fiberscopy was performed and cardiopulmonary resuscitation was given for 45 minutes. He died the next day from fulminans purpura which was secondary to invasive meningococcal infection due to serogroup W135, **meningococcemia** and cardiovascular arrest. Meningococcemic serology was performed on the subject by dosage of bactericidal antibodies using HsBA process (bactericidal activity serum with human complement). All HsBA were equal or superior to protection threshold against invasive meningococcal infection (excepted for Y serogroup of the subject). Serology result was in favor of post vaccination immune response. The meningococcal sero-group W-135 strain isolated from subject blood culture was 2b serotype, subtype P1-5,2 susceptible to Penicillin G (Minimum Inhibitory Concentration, MIC of 0, 125) and to amoxicillin (MIC of 0, 250) belonging to the clonal complex ST-22 and Fet A VR: F3-7. Investigation of complement system of the subject showed C7 homozygote deficit inferior at 10% (normal range was 60-140). The physician concluded that there was constitutional susceptibility of the subject. Only meningococcemia was coded as an event by French health authority which assessed the causality as unlikely (suspected).

PHHY2013US033977 (Lit/HCP): A 20-year-old male subject had a history of fever, headache, body aches, photophobia, neck stiffness, petechiae, lumbar puncture showed pleocytosis and gram-negative diplococcic, rash and platelet count decreased (94 x 10^3/mm3). His cerebrospinal fluid (CSF) cultures showed presence of Neisseria meningitides (diagnosis of **meningococcal meningitis**) at the age of 10 and received treatment with dexamethasone, ampicillin, and meropenem and his CH50 (classical

complement pathway hemolytic assay) was 40 u/Ml (normal range: 31-66). While he was in good health, before vaccination, his complement levels was as followed, C6: 10.4 mg/dL (reference range 7.1–12.8), C7: undetected (reference range 4–11 mg/dl); C8: 19.8 mg/dL (reference range 10.7–24.9) and C9: 31 mg/dL (reference range 6–29). At the age of 19, he was vaccinated with tetravalent polysaccharide Menveo INN. After 10 months of post vaccination (five months before his terminal illness), his serum sample showed IgG levels to capsular polysaccharides as group A capsule: 3.5 mg/mL; group C capsule: less than 0.5 mg/mL; group Y capsule: 0.8 mg/mL and group W-135 capsule: less than 0.5 mg/mL. It was reported complement component 7 was found to be deficient and antibody levels to meningococcal polysaccharides were undetectable for two serogroups and low for the infecting serogroup 10 months post-vaccination. After 15 months of vaccination, he presented to a clinic with one day history of fever, chills, aching in the muscles of his legs, upper back and neck and a pounding frontal headache with light sensitivity. At this initial clinic visit he was diagnosed with a probable viral syndrome, and was prescribed with ibuprofen, and excused from duty for the day. About 8 hours later he developed nausea, vomiting and a generalized purplish macular rash. He said he felt “like he did when he had meningitis.” He visited the emergency room (hospitalization), and had respiratory distress, on his arrival, prompting endotracheal intubation. He presented with symptoms of meningococcal sepsis and started treatment with several broad-spectrum antibiotics, including ceftriaxone, and dexamethasone. His CH50, drawn while he was in the throes of sepsis was 10 U/mL; C3 was low at 62 mg/dL (normal 82–235) and C4 was low at 10 mg/dL (normal 16–70). His blood cultures showed presence of N. meningitides (meningococcal meningitis), which was subsequently shown to be serogroup Y. Despite pressor support, transfusions of fresh frozen plasma and hemodialysis, he expired due to disseminated intravascular coagulation and intracranial hemorrhage on hospital day of 6. The author stated that the anti- capsular IgG (immunoglobulin G) levels of the subject appeared to be modest for group A, but clearly deficient to group C and his antibodies to group W-135 were undetectable and to group Y were clinically inadequate, hence represent the earliest time to vaccine failure in a C7-deficient individual in which the infecting serogroup and prior antibody levels were known. This case highlight the fact that some individuals with terminal complement component deficiencies (TCCD) mount an impaired or short-lived response to vaccination with meningococcal capsular polysaccharides and underscore the appropriateness of a more aggressive vaccination strategy in this patient population.

PHHY2013US116861 (SR-HCP (HA)): A 19-year-old female subject was vaccinated with Menveo INN. At an unspecified amount of time later, she became ill and was hospitalized. The subject was diagnosed with bacterial meningitis. Two days later she died.

Table 3-2 15-Day Non-fatal alerts from Infections and infestations SOC

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHEH2013US010146/SR-HCP (HA)	10/F	Cellulitis/erythema/swelling/feeling hot	Menveo	NA	NA	NA	Unspecified time after vaccination, she experienced raised, warm to touch, softball size reaction. She was diagnosed with cellulitis and was treated with antibiotics. Outcome was not reported.
PHEH2013US015551/SR-HCP (HA)	11/F	Cellulitis/vaccination site erythema/vaccination site swelling/vaccination site induration/body temperature increased	Menveo	NA	NA	NA	Two days after vaccination, the subject experienced redness, swelling, and hardness at the vaccination site and also experienced increased temperature of 100 F. He was diagnosed with cellulitis and was prescribed sulfamethoxazole and trimethoprim. The outcome was not reported.
PHEH2013US016149/SR-HCP (HA)	Unk/ Unk	Cellulitis	Menveo	NA	NA	NA	Unspecified time after vaccination, the subject experienced cellulitis and was treated with antibiotics. The outcome was not reported.
PHEH2013US016359/SR-HCP (HA)	13/M	Cellulitis/extensive swelling of vaccinated limb/erythema/vaccination site warmth/tenderness	Menveo	NA	NA	NA	Two hours after vaccination, he began to experience redness, swelling, and heat at injection site. The symptoms worsened over next 24 hours with tender, firm edema and erythema of skin at acromioclavicular joint. The subject was diagnosed with cellulitis and was treated with antibiotics. He recovered completely.
PHEH201	11/M	Vaccination site	Menveo	NA	NA	NA	The subject was vaccinated with

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
3US021639/SR-HCP (HA)		cellulitis/skin warm/erythema/skin discoloration/Incorrect storage of drug					Menveo which was stored in temperature lower than recommended range. After vaccination, he complained of increased redness in the arms, hot to touch, and pink area of the upper arm that did not help with ibuprofen. He was diagnosed with cellulitis and was treated with sulfamethoxazole and trimethoprim. He recovered completely.
PHFR2012GB006273/SR-HCP	46/M	Cellulitis/local swelling/swelling/pyrexia/malaise/vomiting	Menveo	NA	NA	NA	Forty eight hours after vaccination, the subject experienced severe swelling of the left arm and chest wall with fever, sickness, and vomiting which required treatment with prednisone and antibiotics. He was diagnosed with cellulitis. The subject completely recovered.
PHHO2010US06190/CT-HCP	9 months/M	Groin abscess/cellulitis/lymph node abscess/staphylococcus test positive/erythema/lymphadenitis/pyrexia/necrosis/pain/edema/inguinal mass/swelling	Men ACWY and conjugate vaccine	NA	Lymphnode Abscess/viral infection/family history of stroke	Inactivated polio vaccine/influenza vaccine/pneumococcal conjugate vaccine/diphtheria, hemophilus influenza vaccine, pertussis, and tetanus vaccine/rotavirus vaccine	The subject was vaccinated with three doses of study vaccine. Approximately three months after last dose, the subject presented to emergency room with sudden swelling in the left inguinal region. The subject had presented increasing fussiness and swelling. Ten day prior to this episode subject had viral syndrome with fever followed by a full body rash and received paracetamol. Upon examination of inguinal area large amount of edema and erythema was noted which was tender and firm. Left inguinal abscess and left groin cellulitis was diagnosed.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
							Culture was positive for methicillin resistant staphylococcus. The subject received intravenous antibiotics initially and later had abscess drainage. The subject completely recovered. The investigator suspected a causal relationship between the event and vaccine.
PHHY2012US038069/SR-HCP	15/F	Cellulitis/erythema/swelling/pain/pruritus	Menveo	NA	Hypersensitivity to sulfa drugs and attention deficit/hyperactivity disorder	NA	Unspecified time after vaccination, the subject experienced redness, swelling, severe itching, pain and cellulitis. She was treated with diphenhydramine hydrochloride and recovered completely.
PHHY2013AR000974/SR-HCP	8/M	Cellulitis/inflammation/erythema/mobility decreased/vaccination site swelling/vaccination site erythema/petechiae/extensive swelling of vaccinated limb	Menveo	NA	NA	NA	One day after vaccination, the subject presented with erythema and swelling at the site of application comprising the shoulder region. He had inflammation of the shoulder region to the middle of the arm which was very red. He had cellulitis along with petechiae. He received cephalexin. Forty eight hours after vaccination, the subject still had local involvement and loss of function. He was further treated with amoxicillin and clavulanate and sulfamethoxazole and trimethoprim. He recovered completely.
PHHY2013AR04811	5/M	Meningitis viral/headache/vom	Menveo	NA	Streptococcal	NA	Approximately 15 months after vaccination, the subject was

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
7/SR-HCP		iting/pyrexia/head injury			pharyngitis		hospitalized with severe headache, pyrexia, and vomiting for 24 hours. After examination, he was diagnosed with viral meningitis and was treated with penicillin, metamizole, diclofenac, midazolam, and lactate ringer. He recovered completely
PHHY2013AR119138/SR-HCP	4/F	Vaccination site cellulitis/vaccination site edema/vaccination site induration/pyrexia/injection site discoloration	Menveo	NA	NA	NA	One day after vaccination, subject presented with fever and tumefaction affecting three quarters of the upper limb. The physician suspected cellulitis and treated her with cephalexin and later with intravenous clindamycin and diphenhydramine. She recovered completely.
PHHY2013BE082220/SR-HCP	19/F	Meningitis aseptic/meningism/pyrexia/CSF white blood cell count increased	Menveo	NA	Protein C deficiency/meningitis	Meningococcal vaccine	She experienced the first episode of what seemed to be aseptic meningitis with meningitis like symptoms including high temperature (39 degree Celsius) and meningeal syndrome five months after vaccination and high dose antibiotics were started immediately. After laboratory examinations, she was diagnosed with aseptic meningitis. She was treated with ceftriaxone, ampicillin and aciclovir. Later she had a second episode of aseptic meningitis and was hospitalized again and treated with same medications. She recovered completely. The physician did not suspected Menveo either for lack of efficacy or adverse event.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHHY2013BR082627/SR-HCP	47/F	Vaccination site infection/migraine/edema/vaccination site pain/vaccination site erythema/pain/pyrexia	Menveo	NA	NA	NA	Same day after vaccination, the subject experienced pain and redness at vaccination site. She also had edema, body pain, migraine, and fever at night. She had infection at vaccination site. She recovered from fever.
PHHY2013BR083257/SR	10/M	Cellulitis/extensive swelling of vaccinated limb/skin warm/induration/erythema/pyrexia	Menveo	NA	NA	NA	Six hours after vaccination, the subject experienced warmth, edema, and induration, redness at vaccination site which extended to entire arm and also had fever. He was diagnosed with extensive cellulitis and received cephalexin. He recovered completely.
PHHY2013FR143221/SR-HCP	24/M	Dermo-hypodermatitis/pyrexia	Menveo	Measles, mumps, and rubella vaccine	NA	NA	One day after vaccination, he experienced fever and dermo-hypodermatitis on two ankles leading to hospitalization. The subject was improving.
PHHY2013IT108780/SR-HCP	48/M	Meningitis/nuchal rigidity/photophobia/eye movement disorder/hyperpyrexia/muscle rigidity/headache/bladder spasm	Menveo	NA	NA	NA	Nine days after vaccination, the subject experienced intense frontal headache, intense photophobia, difficult on ocular movement, hyperpyrexia and vesical tenesmus, mild nuchal and low back rigidity. On the same day, he was diagnosed with meningeal phlogosis and was hospitalized. He was treated with ceftriaxone, aciclovir, and cortisone. The subject was improving.
PHHY201	Unk/	Cellulitis/pyrexia/pa	Menveo	NA	NA	NA	Three days after vaccination, the

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
3MY026000/SR-HCP	F	in					subject experienced pain and fever in the morning and also experienced cellulitis on the same day. She was treated with antibiotics and was improving.
PHHY2013SE102101/SR-HCP	Unk/F	Soft tissue infection/extensive swelling of vaccinated limb/skin warm/pyrexia/pain in extremity/pain/hypersensitivity	Menveo	NA	Rheumatic disorder	Prednisolone/methotrexate	Two days after vaccination, she experienced fever, sever swelling, and heat in the left arm. She experienced pain and swelling on the arm and the pain radiated to breast and axilla and was hospitalized. She was diagnosed with soft tissue infection and received intravenous antibiotics for treatment. Outcome was not reported.
PHHY2013US012273/SR-HCP (HA)	14/F	Cellulitis/tenderness/pain in extremity/erythema/skin warm	Menveo	Hepatitis A vaccine/human papilloma vaccine	NA	NA	One day after vaccination, the subject experienced left arm pain, erythema, the area was warm, which was tender upon palpation. She was diagnosed with cellulitis. Outcome was unchanged.
PHHY2013US012483/SR-HCP (HA)	11/M	Vaccination site cellulitis/vaccination site warmth/vaccination site erythema	Menveo	Influenza vaccine	NA	NA	Two days after vaccination, the subject developed cellulitis down the left deltoid which was approximately 13x14 cm. The area was warm and red. He was treated with cold compress and diphenhydramine hydrochloride. Outcome was unchanged.
PHHY2013US012483/SR-HCP (HA)	11/M	Vaccination site cellulitis/vaccination site swelling/vaccination site erythema	Menveo	Influenza vaccine/human papilloma vaccine/diphtheria, tetanus,	NA	NA	One day after vaccination, the subject experienced acute swelling of left deltoid area (vaccination site) with erythema. He visited emergency room and was diagnosed with cellulitis and

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
				and pertussis vaccine			treated with oral clindamycin. He recovered completely.
PHHY2013US042539/Lit-HCP	Unk/F	Meningitis aseptic/meningococcal sepsis	Menveo INN	NA	Neuromyelitis optica	NA	Despite vaccination, the subject developed meningococcal septicemia with sterile meningitis which readily responded to antibiotic treatment.
PHHY2013US044455/SR-HCP (HA)	11/M	Cellulitis/vaccination site erythema/vaccination site warmth/vaccination site pain	Menveo	Diphtheria, tetanus, and pertussis vaccine	NA	NA	One day after vaccination he experienced erythema, heat and tenderness at left deltoid region. He also experienced mild erythema at the injection site. On the same date, he also experienced cellulitis and received treatment with cephalexin. The symptoms worsened on day 2 after immunization and he visited emergency room. The outcome of the events was reported as recovered.
PHHY2013US083983/SR-HCP (HA)	11/M	Vaccination site cellulitis	Menveo	Diphtheria, tetanus, and pertussis vaccine	NA	NA	Twenty four hours after vaccination, he developed slight cellulitis in the application site of Menveo. He was given cold compress and diphenhydramine. He recovered completely.
PHHY2013US084005/SR-HCP (HA)	11/M	Vaccination site cellulitis/vaccination site pruritus/vaccination site erythema/pyrexia/vaccination site pain	Menveo	Human papilloma vaccine	NA	NA	Immediately after vaccinations, the subject experienced redness at vaccination site which progressed. He also developed pain, itching at vaccination site and fever. He was diagnosed with cellulitis and was treated with cephalexin and diphenhydramine. He recovered

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
							completely.
PHHY2013US084023/SR-HCP (HA)	17/F	Vaccination site cellulitis/vaccination site warmth/vaccination site dryness/vaccination site rash/vaccination site erythema/vaccination site urticaria/vaccination site swelling/vaccination site pain/dermatitis allergic	Menveo	Human papilloma vaccine/diphtheria, tetanus, and pertussis vaccine	Iron deficiency anemia/asthma exercise induced	Beclometasone/docusate/ciprofloxacin/ibuprofen/paracetamol/salbutamol/ferrous sulfate	Three days after vaccination she experienced skn warmth, dryness, rash, erythema, and hive like rash at the vaccination site. The site was tender and the area was slightly raised. She was diagnosed with cellulitis and dermatitis allergic. She recovered completely.
PHHY2013US097367/SR-HCP (HA)	26/F	Cellulitis/edema/pain/erythema/vaccination site rash/dyspnea/nausea/vomiting	Menveo	NA	NA	NA	Same day after vaccination, she noticed a rash around the site. Two days later she experienced extreme pain, edema, and erythema. She took ibuprofen but did not have relief. She also experienced nausea, vomiting, and shortness of breath. She was diagnosed with cellulitis and was treated with sulfamethoxazole and trimethoprim. She recovered completely.
PHHY2013US127698/SR-HCP	35/F	Cellulitis/chills/pyrexia/hypersensitivity/ vaccination site	Menveo	NA	NA	Simvastatin/sulfamethoxazole, trimethoprim/pant	Two days after vaccination, her injection site became very red and sore. She was treated with antibiotic. She also

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
(HA)		erythema/vaccination site pain				oprazole/levothyroxine/doxycycline/solifenacin	had chills and fever and was diagnosed with cellulitis and was hospitalized. She was treated with oral antibiotics and was doing well.
PHHY2013US127701/SR-HCP (HA)	43/M	Vaccination site cellulitis	Menveo	Pneumococcal vaccine/varicella vaccine/diphtheria, tetanus, and pertussis vaccine	Iodine allergy	Propranolol/hydroxyzine embonate	Two days after vaccinations, the subject developed cellulitis at vaccination site and was treated with antibiotics. She recovered completely.
PHHY2013US127821/SR-HCP (HA)	11/M	Vaccination site cellulitis/vaccination site erythema/vaccination site urticaria/vaccination site pruritus/vaccination site pain/vaccination site warmth/pain in extremity/hypersensitivity/erythema	Menveo	Human papilloma vaccine/diphtheria, tetanus, and pertussis vaccine	NA	NA	Two days after vaccination, the subject was taken to emergency room for red painful arm. He also developed redness, welts, itching, pain, and warmth at vaccination site. He was diagnosed with cellulitis at vaccination site and allergic reaction. He recovered completely.
PHHY2013US140156/SR-HCP (HA)	17/F	Vaccination site cellulitis/vaccination site erythema/vaccination site pain/vaccination site swelling	Menveo	Influenza vaccine	Allergic rhinitis/eczema	NA	Two days after vaccination, she experienced a large area of redness, pain, and swelling at right upper arm involving half of her upper outer arm. She was diagnosed with cellulitis and was treated with cephalexin. She recovered completely.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHHY2014US000732/SR-HCP (HA)	11/M	Skin infection/upper extremity mass/erythema/pain in extremity/swelling/hypersensitivity	Menveo	Influenza vaccine/hepatitis A vaccine/human papilloma vaccine/diphtheria, tetanus, and pertussis vaccine	Autism	NA	One day after vaccination, he developed a raised red lump on the left arm with pain. He also had swelling. Redness began to spread. He was treated with cephalexin for suspected skin infection. Later he was also prescribed prednisone for allergic reaction. He recovered completely.

*SR=Spontaneous report, CT=Clinical Trial, HCP=Health care professional, M=Male, F=Female, HA=Health Authority, NA=Not Applicable

3.9 Injury, poisoning and procedural complications

During this review period, a total of 442 adverse events from 421 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events identified were contusion, fall, head injury, laceration, lip injury, and tooth fracture. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2012US098974 (SR-HCP (HA)): A 12 year old male subject was vaccinated with Menveo, diphtheria, pertussis, and tetanus vaccine and varicella vaccine. After vaccinations the subject fainted and as he fell, his tooth struck on door leading to **chipping front tooth**. Cold compress was given to the subject (ice pack). The outcome of the event was recovered.

3.10 Investigations

During this review period, a total of 35 adverse events from 32 case reports were identified under this body system. Of these, 17 were serious unlisted events. The serious unlisted events identified were blood creatinine increased, blood pressure decreased, body temperature increased, CSF white blood cell count decreased, complement factor decreased, heart rate decreased, hepatic enzyme increased, platelet count decreased, pulse absent, respiratory rate decreased, Staphylococcus test positive, and synovial fluid analysis abnormal. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2012US099136 (SR-HCP (HA)): A 17-year-old female subject was vaccinated with Menveo, human papilloma vaccine, polio vaccine, measles, mumps, and rubella vaccine, and diphtheria, pertussis, and tetanus vaccine and varicella vaccine. On the same day she became pale and lost consciousness briefly but did not fall and was able to walk to the bed. **Blood pressure was 90/70**. She was awake oriented, but continued to feel weak and nauseous. She was moved to the hospital. The final outcome of the event was recovered.

PHHY2013US127758 (SR-HCP (HA)): An 18-year-old male subject was vaccinated with Menveo, human papilloma vaccine, and measles/mumps/rubella vaccine. On the same day, after vaccination, he became diaphoretic and developed dizziness and blurred vision. And his **blood pressure was reported as 74/42**, 84/44 and 110/54. This was atypical reaction for this subject. Outcome of the events was reported as recovered on the same day.

3.11 Metabolism and nutrition disorders

During this review period, a total of five adverse events from four case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were acidosis and dehydration. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and

therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2013US127756 (SR-HCP (HA): An 11-year-old female subject whose historical drugs included penicillin and azithromycin and had allergies with them was vaccinated with Menveo, human papilloma virus vaccine, and tetanus/diphtheria/pertussis vaccine. One day after vaccination she experienced abdominal pain, vomiting with increased eosinophil count. Extensive work up done and complete blood count differentiation showed eosinophil increased, and urine analysis showed ketones. The subject progressed to **dehydration** and was hospitalized. She was mildly acidotic and no diagnosis could be made. The outcome of the events was reported as complete recovery.

3.12 Musculoskeletal and connective tissue disorders

During this review period, a total of 101 adverse events from 83 case reports were identified under this body system. Of these, 35 were serious unlisted events. The serious unlisted events identified were arthralgia, back pain, flank pain, inguinal mass, joint range of motion decreased, mobility decreased, muscle rigidity, muscle spasms, muscular weakness, musculoskeletal stiffness, myalgia, myositis, neck pain, nuchal rigidity, pain in extremity, posture abnormal, synovitis, and upper extremity mass. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHEH2013US010862 (SR-HCP): A 27 year old male subject was vaccinated with Menveo. Within 24-48 hours after receiving vaccination, he developed high fever greater than 103 degrees, **neck stiffness**, and headaches. He went to the ER due to the events. He was hospitalized under the suspicion of meningitis where he was followed-up by an infectious disease physician. Lumbar puncture, spinal tap, x-rays, and laboratory testing were performed in ER, for which all results were negative for any infectious disease. He recovered completely. He stayed in hospital for two to three days and was discharged in stable condition. The infectious disease physician mentioned that the vaccine possibly caused the symptoms.

PHHY2012DE118064 (SR-HCP (HA)): A 25-year-old female subject was vaccinated with Menveo and typhoid vaccine. Same day after vaccinations, she presented with flank pain and **back pain** lasting for one day. She was hospitalized due to these events. The final outcome was reported as completely recovered.

PHHY2013AR038179 (SR-HCP): A 4-year-old female subject was vaccinated with Menveo. On the same date, within 24 hours after vaccination the subject experienced local symptoms of pain, heat and tumefaction at the application site. Twenty four hours after vaccination she experienced pain in right thigh and functional impotence. On the same date, her hip echography (ultrasound) showed increase in synovial liquid which was diagnosed as **sinovitis** in right hip. She had a clinical improvement with persistent mild discomfort in right leg. The outcome of the events was completely recovered without sequelae. The evolution was favorable; subject rested and took non-steroidal anti-inflammatory drugs.

PHHY2013DE035340 (SR-HCP (HA)): A 41-year-old male subject was vaccinated with the first dose of Menveo. On the same date, post vaccination he experienced headache, **neck pain**, local reaction, injection site joint movement impairment, myalgia and pain in limb/pain in extremities. He was hospitalized due to these events. The events were also assessed as medically significant. He was treated with antiphlogistic drugs (unspecified), bromelaine, rutosid trihydrate and trypsine and ibuprofen. The symptoms were improved, but had not completely recovered.

PHHY2013FR108513 (SR-HCP (HA)): A 20-year-old male subject was vaccinated with Menveo and diphtheria/tetanus/pertussis/poliomyelitis vaccine. The following night after vaccination, he experienced "**painful contraction of both triceps**". When he visited the physician, elbow flexion from 90 degree and internal rotation of shoulders were impossible. He experienced nothing special at the shoulder muscle level. As a result of these events, he was unable to follow the military instructions for five days which required the use of upper limbs. He recovered completely later. Health Authority assessed the causality of the events as related to the administration of vaccines. The Health Authority reported the seriousness of the events as 'disability'.

PHHY2013US012247 (SR-HCP (HA)): An 11-year-old male subject with medical history of gastro-esophageal reflux and hyperlipidemia was vaccinated with Menveo. One day after vaccination, the child complained of **bilateral leg weakness** and the condition worsened progressively. He was admitted to hospital for five days and received two doses of intravenous immunoglobulin. His symptoms improved following the treatment. He visited the emergency room (ER) following this reaction. Final outcome was reported as condition unchanged.

3.13 Nervous system disorders

During this review period, a total of 272 adverse events from 183 case reports were identified under this body system. Of these, 69 were serious unlisted events. The serious unlisted events identified were acute disseminated encephalomyelitis, altered state of consciousness, ataxia, autonomic nervous system imbalance, balance disorder, benign intracranial hypertension, cerebral disorder, chronic inflammatory demyelinating polyradiculoneuropathy, convulsion, dizziness, dyskinesia, encephalitis, epilepsy, febrile convulsion, grand mal convulsion, Guillain-Barre syndrome, hemorrhage intracranial, headache, hypoesthesia, hypotonia, IIIrd nerve paralysis, loss of consciousness, meningism, migraine, paresthesia, presyncope, seizure like phenomena, syncope, tonic clonic movements, tremor, unresponsive to stimuli, and VIIth nerve paralysis. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

Table 3-3 15-Day alerts from the Nervous system disorders SOC

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHEH2013US005126/SR-HCP (HA)	12/F	Autonomic nervous system imbalance/orthostatic hypotension/dizziness/myositis/myalgia/ataxia/migraine/headache/muscular weakness/vision blurred/stress/anxiety	Menveo	Diphtheria, tetanus and pertussis vaccine	Migraine	NA	Twenty five days after vaccination with Menveo and diphtheria, tetanus and pertussis vaccine, the subject experienced dizziness, blurred vision, and felt faint at school. She had headache and lower limb weakness and was taken to emergency room and was treated with ibuprofen and intravenous fluids. She had high levels of anxiety and stress. She was diagnosed with atypical migraine, orthostatic hypotension dysautonomic syndrome, ataxia, myalgia, and post infectious myositis. Her condition improved.
PHEH2013US008149/SR-HCP (HA)	Unk/ Unk	Encephalitis	Menveo INN	NA	NA	NA	Unspecified date after vaccination, the subject developed encephalitis. The physician suggested that the event was temporally associated with meningitis vaccination.
PHEH2013US012492/SR-HCP (HA)	17/F	Dizziness/nausea	Menveo	NA	NA	NA	Next day after vaccination, the subject experienced intermittent nausea and dizziness which lasted one hour at a time which was debilitating the subject. The outcome was condition persisting.
PHEH2013US014802/SR-HCP (HA)	12/M	Loss of consciousness	Menveo	Diphtheria, tetanus and pertussis vaccine	NA	NA	Ten minutes after vaccination, the subject passed out.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHEH2013US016133/SR-HCP (HA)	12/M	Syncope	Menveo	Varicella virus vaccine/human papilloma vaccine	NA	NA	The subject was vaccinated with Menveo in the left deltoid, varicella vaccine in the right arm and human papilloma vaccine in the right deltoid. Same day after vaccination he fainted and was treated with ammonia, and was given popsicle. He recovered after 30 minutes.
PHEH2013US017479/SR-HCP (HA)	17/M	Syncope	Menveo	Hepatitis A vaccine	NA	NA	Two minutes after receiving both Menveo and hepatitis A vaccine, the subject fainted. He recovered on the same day.
PHEH2013US018639/SR-HCP (HA)	18/Unk	Syncope/wrong technique in drug usage process	Menveo	Hepatitis A vaccine	NA	NA	The subject received only Men A lyophilized conjugate component of Menveo which was accidentally constituted with sterile water instead of Men C, Y, W-135 liquid conjugate. The subject also received hepatitis A vaccine. Same day after vaccinations, the subject experienced vasovagal syncope and recovered on the same day.
PHEH2013US019091/SR-HCP (HA)	Unk/F	VIIth nerve paralysis/skin sensitization/vision blurred/exaphthalmos/vomiting/headache	Menveo	NA	NA	NA	Same day after vaccination, the subject experienced headache and vomiting. Next day, she experienced facial droop. Two days later she had blurred eye vision in the right eye and later she had proptosis. The next day she was treated with methylprednisolone, eye drops, and vitamin B. She recovered from facial droop but right side of the face was very sensitive.
PHEH2013US01915	Unk/F	Loss of consciousness/lac	Menveo	NA	NA	NA	Immediately after vaccination, she lost consciousness, falling and sustained a

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
8/SR-Non HCP (HA)		eration/head injury/fall					laceration to her right hand which required ten stitches and sustained a head injury.
PHEH2013US020576/SR-Non-HCP (HA)	Unk/M	Loss of consciousness/tooth fracture/lip injury/Fall	Menveo	NA	NA	NA	Same day after vaccination, he passed out striking the floor. He sustained a comminuted fracture in the extra osseous portion of the right upper center incisor and displacement of minor fragments anteriorly to the upper lip soft tissue.
PHEH2013US020873/SR-HCP (HA)	18/M	Syncope	Menveo	NA	NA	NA	Unspecified time after vaccination, the subject fainted and had to go to the hospital. Menveo was suspected to cause the event.
PHEH2013US024411/SR-HCP	11/M	Syncope/fall	Menveo	NA	NA	NA	Same day after vaccination he fainted and fell. The outcome was not reported.
PHEH2014US001741/SR-HCP	11/M	Syncope/unresponsive to stimuli/vital functions abnormal/blood pressure decreased/abdominal pain upper	Menveo	NA	NA	NA	Two minutes after the vaccination, he experienced stomach pain. Shortly after that he fainted and remained unresponsive for ten minutes. His vital signs appeared slightly lower than normal. Blood pressure was 80/50 mmHg. He was given oxygen. He recovered and was discharged in a stable condition.
PHHO2009US17236/CT-HCP	7 Months/M	Febrile convulsion/otitis media/diarrhea	MenACWY and conjugate vaccine			Diphtheria, hepatitis B, pertussis, poliomyelitis, and tetanus vaccine/rotavirus vaccine/dipht	Approximately 162 days after vaccination, the subject experienced otitis media, diarrhea, and febrile seizure for six minutes. The subject was placed on oxygen and treated with paracetamol and intravenous antibiotics and was hospitalized. The subject recovered completely.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
						heria, pertussis, tetanus, poliomyelitis, and haemophilus B conjugate vaccine/pneumococcal vaccine/hepatitis B vaccine/haemophilus conjugate B vaccine	
PHHO2010US05822/CT-HCP	6 months/F	Epilepsy/presyncope/convulsion/foaming at mouth/cyanosis/tremor/muscle rigidity/musculoskeletal stiffness/vomiting/ viral diarrhea	MenACWY and conjugate vaccine	NA	NA	Diphtheria, pertussis, tetanus, poliomyelitis/ haemophilus B conjugate vaccine/rotavirus vaccine/pneumococcal conjugate vaccine/hepatitis B vaccine	Approximately 140 days after vaccination, the subject experienced vasovagal episode. The subject also experienced vomiting and viral diarrhea and was hospitalized. Approximately two months later the subject experienced seizure disorder with foaming from the mouth, blue lips, shaking and the subject was rigid. The event lasted 2-3 minutes and she was taken to the emergency room. The subject was evaluated and was diagnosed with epilepsy. The investigator suspected a causal relationship between the epilepsy and vaccine. The other events were not suspected to the vaccine.
PHHO2010US12183	13 mont	Acute disseminated	MenACWY and	NA	NA	Influenza vaccine/hepa	The subject received four doses of study vaccine. Twenty days after the last dose, the

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
/CT-HCP	hs/M	encephalomyelitis/ataxia/cerebral disorder	conjugate vaccine			titis A vaccine/measles, mumps, and rubella vaccine/pneumococcal vaccine/rotavirus vaccine/hepatitis B vaccine/H1N1 vaccine/diphtheria, tetanus, pertussis, poliomyelitis, haemophilus B conjugate vaccine	subject experienced ataxia and was hospitalized. Examinations revealed abnormal white matter in the periventricular areas posteriorly. The results were consistent with acute disseminated encephalomyelitis. The subject dropped out of the study due to the event. He was treated with pulse steroids which showed improvement. The investigator suspected a causal relationship between the event and the vaccine.
PHHY2012IT116219/SR-HCP	12/M	Tonic clonic movements/agitation/asthenia/vertigo	Menveo	NA	NA	Cetrizine hydrochloride	Ten minutes after vaccination, the subject experienced vertigo with hyposthenia at lower limbs. Forty minutes later, he experienced tonic clonic contractions of the facial muscles and also the upper limb muscles and experienced general state of agitation and he was taken to the emergency room. The outcome was condition improving and the causality was suspected.
PHHY2012US09908	18/F	Loss of consciousness/vo	Menveo	NA	NA	NA	The subject passed out after receiving vaccine. She was revived two minutes later.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
7/SR-HCP		miting					She threw up and passed out again. She was revived again. Twenty minutes later she recovered.
PHHY2012US110985/SR-HCP	15/M	Guillain-Barre syndrome	Menveo	NA	NA	NA	Fifty five days after vaccination, the subject experienced Guillain-Barre syndrome and was hospitalized. He recovered completely.
PHHY2012US111726/SR-HCP	11/F	Loss of consciousness	Menveo	Diphtheria, tetanus, and pertussis vaccine/varicella vaccine/human papilloma vaccine	NA	NA	The subject received Menveo and human papilloma virus vaccine in the left arm and diphtheria, tetanus and pertussis vaccine and varicella vaccine in the right arm. Same day after vaccinations, the subject passed out. She recovered on the same day.
PHHY2013AR042489/SR-HCP	Unk/ F	Presyncope/tonic convulsion/hypertonia/visual impairment/nerve stimulation test abnormal/disorientation/mydriasis	Menveo	NA	NA	NA	Same day after vaccination, the subject experienced lipothymy, with partial recuperation by placing in supineposition and by administering oral liquids. Fifteen minutes later she experienced generalized hypertonia with retroversion of sight and no sphincter relaxation nor response to administration for one and a half minute. She was also found to be be disoriented in time and space with mydriatic pupils for about two minutes. The subject was hospitalized due to the events and was treated with oxygen. She recovered completely.
PHHY201	46/F	Tremor/headache/	Menveo	NA	Paroxysmal	Eculizumab	On the same day after vaccination, the

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
3DE005106/SR-HCP		malaise			nocturnal hemoglobinuria		subject experienced headache, trembling, and malaise and was hospitalized for two days. She recovered eight days later.
PHHY2013GR004625/SR-HCP	12/M	Meningism/headache/vomiting/photophobia/pyrexia/leukocytosis/granulocytosis	Menveo	NA	NA	NA	Ten-thirteen days after vaccination he experienced headache, vomiting, fever, and mild meningeal irritation signs and photophobia. He was referred to hospital and examinations revealed leukocytosis and mild granulocytosis. He was treated with amoxicillin and clavulanate as a precaution. The subject recovered 12 hours later.
PHHY2013KR038876/SR-HCP	19/M	Guillain-Barre syndrome/VIIth nerve paralysis/muscular weakness/gait disturbance/dysphagia	Menveo	Measles, mumps, and rubella vaccine/tetanus and diphtheria vaccine	Upper respiratory tract infection	NA	Within one month after vaccination, the subject experienced limb weakness and facial paralysis. Later the weakness aggravated and additionally, walking difficulty and dysphagia were revealed and the subject was transferred to a hospital. He was diagnosed with Guillain-Barre syndrome and was treated with intravenous immunoglobulins. Since the subject had a history of upper respiratory tract infection prior to vaccination, a causal relationship was not confirmed yet. The outcome was ongoing.
PHHY2013KR082715/SR-HCP	Unk/M	Guillain-Barre syndrome	Menveo	Tetanus vaccine/measles, mumps, and rubella vaccine	Keratomileusis	NA	Twelve days after vaccination, the subject experienced symptoms of ascending paralysis and was hospitalized and was diagnosed with Guillain-Barre syndrome. The subject was still hospitalized.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHHY2013US000482/SR-HCP	23/M	Hypoesthesia/diarrhea/eye color chage/hyperhidrosis/dizziness/nausea/vomiting/pyrexia/vaccination site erythema/vaccination site swelling	Menveo	NA	NA	NA	On the same day after vaccination, the subject experienced sweating, lightheadedness, nausea, vomiting, diarrhea, fever and numbness throughout his body. His eyes were white without normal cooling. The subject also had vaccination site swelling and redness. The outcome was condition unchanged.
PHHY2013US000552/SR-HCP	11/M	Syncope/pallor/fall	Menveo	Varicella virus vaccine/diphtheria, tetanus, and pertussis vaccine/influenza vaccine/hepatitis A vaccine	NA	NA	Same day after vaccination, the subject fainted and fell out of chair and was pale. The events lasted for a minute.
PHHY2013US000608/SR-HCP	17/M	Seizure like phenomena/posture abnormal/dyskinesia/pallor/asthenia	Menveo	Hepatitis A vaccine/influenza virus vaccine/polio vaccine	Cough	NA	Same day after vaccination, the subject's head dropped and appeared to slump forward after last shot was given. Two jerks and seizure like activity was observed in right arm and chest. He was weak and complexion was pale. He was seated in a chair with legs elevated. His complexion improved and he recovered completely.
PHHY2013US01220	32/F	Loss of consciousness/unresponsive to	Menveo	Human papilloma vaccine/dip	NA	NA	On the same day after vaccination, the subject experienced dizziness and passed out and was unresponsive for two to three

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
2/SR-HCP		stimuli/dizziness		htheria, tetanus, and pertussis vaccine			minutes. The subject had not yet recovered.
PHHY2013US032529/SR-HCP	16/F	Guillain-Barre syndrome/chronic inflammatory demyelinating polyradiculoneuropathy/asthenia/paresthesia/benign intracranial hypertension	Menveo	Diptheria, tetanus, and pertussis vaccine	NA	NA	Two weeks after vaccination the subject experienced tingling in feet and sides of hands and was taken to the local hospital and was treated with intravenous immunoglobulins and was sent home with steroids. Two months later she experienced progressive weakness and admitted in the hospital with Guillain-Barre syndrome and was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy. She was also diagnosed with pseudo tumor of brain due to steroids. The events were assessed as life-threatening. The outcome was condition unchanged.
PHHY2013US032593/SR-HCP	18/F	Loss of consciousness/dizziness	Menveo	Human papilloma vaccine	NA	Levothyroxine sodium/ethinylestradiol, norgestimate	Same day after vaccination the subject became lightheaded and passed out. The subject recovered completely.
PHHY2013US032687/SR-HCP	16/M	Convulsion/syncope/hypotonia/musculoskeletal stiffness	Menveo	Influenza vaccine	Mild mental retardation/autism	NA	Four days after vaccination, the subject experienced stiff arm for one minute while he was flopping his arm and then his hand became claw. He also experienced fainting seizure. He recovered completely after taking to emergency room.

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
PHHY2013US044492/SR-HCP	11/M	Loss of consciousness/dizziness	Menveo	Influenza vaccine/diphtheria, tetanus, and pertussis vaccine/human papilloma vaccine	NA	NA	On the same day after vaccination, he was dizzy and passed out. He recovered completely later.
PHHY2013US056725/SR-HCP	12/M	Altered state of consciousness/dizziness	Menveo	Human papilloma vaccine/diphtheria, tetanus, and pertussis vaccine	NA	NA	Two minutes after vaccinations, the subject experienced dizziness and had change in level of consciousness and was taken to emergency room. He recovered completely.
PHHY2013US069304/SR-HCP	12/F	Dyskinesia/loss of consciousness/confusional state/pallor/fall	Menveo	Diphtheria, tetanus and pertussis vaccine/human papilloma vaccine	NA	NA	Thirty to forty five seconds after vaccination, she began jerking, passed out and fell out of chair. She was given juice and cool towel for head. She woke up in confusional state and was pale, but she was alert. She was observed for 20 minutes and was sent home. She recovered completely.
PHHY2013US069304/SR-HCP	18/M	Dyskinesia/muscle rigidity/musculoskeletal stiffness/eye movement disorder/fall/dizzin	Menveo	Influenza vaccine/human papilloma	NA	NA	Same day after vaccination, he felt dizzy and fell backward in the chair. His eyes rolled back into the lids and body became stiff and rigid. Then jerking rhythmical movements

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
		ess		vaccine			started. He recovered completely.
PHHY2013US097420/SR-HCP	18/F	Convulsion/heart rate decreased/dizziness/nausea	Menveo	NA	NA	Ethinylestradiol, etynodiol diacetate	Immediately after vaccination, she became dizzy. She started to seize for less than a minute. Her blood pressure was 107/85 and she was nauseous. She had not yet recovered.
PHHY2013US127783/SR-HCP	12/M	Presyncope/loss of consciousness	Menveo	Human papilloma vaccine/hepatitis A vaccine	NA	NA	On the same day after vaccinations, he experienced vasovagal reaction and loss of consciousness for seconds. He recovered completely.
PHHY2013US127852/SR-HCP	20/M	Presyncope/loss of consciousness/blood pressure decreased/unresponsive to stimuli/hyperhidrosis/pallor/dry skin/skin warm	Menveo	Unk	Unk	Tuberculin PPD	Five minutes after the vaccination, the subject became pale and passed out in chair. He was unresponsive and became sweaty. He was given a popsicle. He became pink, warm, and skin became dry. The subject felt it was a vasovagal reaction. The subject recovered on the same day.
PHHY2013US127889/SR-HCP	18/M	Grand mal convulsion	Menveo	Human papilloma vaccine	Convulsion/attention deficit/hyperactivity disorder	Lamotrigine/ methylphenidate hydrochloride	Two days after vaccination, he had a two and a half minute grand mal seizure. He was at home and remained there. The event was due to the human papilloma vaccine. He recovered completely.
PHHY2013US147774/SR-HCP	20/F	IIIrd nerve paralysis/eye movement disorder/mydriasis/blepharospasm/b	Menveo	NA	NA	NA	Eighteen days after vaccination, she felt dizzy and complained of eyes spinning around. Later she was lurching to the left, left eye was twitching, and pupil was small with the right pupil large and she was taken to the

Case ID / Report type	Age/ Gender	Reported event Term	Vaccine	Co-suspect vaccine/Drugs	Relevant history	Concomitant medications	Description
		alance disorder/vertigo/dizziness					emergency department. She was diagnosed with right oculomotor nerve palsy. She was treated with prednisone. She recovered completely.

*SR=Spontaneous report, CT=Clinical trial, HCP=Health care professional, M=Male, F=Female, HA=Health Authority, NA=Not Applicable

3.14 Pregnancy, puerperium and perinatal conditions

During this review period, there were no serious/unlisted events reported in this SOC.

3.15 Psychiatric disorders

During this review period, a total of 16 adverse events from 14 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events identified were abnormal dreams, agitation, anxiety, confusional state, mental disorder, and stress. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2013KR038921 (SR-HCP): A male subject of unspecified age with a history of common cold for one week was vaccinated with Menveo. He was hospitalized the next day and diagnosed with **psychological disorder**; conversion disorder was ruled out. Five days later the physician confirmed that the subject did not meet criteria for Guillain-Barre syndrome. He stayed in the hospital for psychiatric follow-up. Causality and outcome of psychological disorder were not reported.

3.16 Renal and urinary disorders

During this review period, a total of four adverse events from four case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were bladder spasm, pyuria, and urinary incontinence. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

3.17 Respiratory, thoracic and mediastinal disorders

During this review period, a total of 51 adverse events from 35 case reports were identified under this body system. Of these, 11 were serious unlisted events. The serious unlisted events identified were apnea, cough, dyspnea, epistaxis, hemoptysis, increased viscosity of nasal secretion, pharyngeal hematoma, pulmonary congestion, and respiratory distress. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHEH2013US003303 (SR/HCP): An 11-year-old female subject was vaccinated with Menveo. Two hours after vaccination, she complained of numbness and tingling of both arms and legs with a temperature of 100-101. Next day, she had an episode of **epistaxis** with blood tinged phlegm (which could be a post nasal drip as per reporter), joint pain of arms and legs.

Two days later, tingling continued, chest congested with mucoid cough and body temperature was 100-103. She was treated with paracetamol. The outcome of the events was not reported.

PHEH2013US016985 (SR/HCP (HA)): An 11-year-old male subject was vaccinated with Menveo along with hepatitis A vaccine. He reported sore arm and 'did not feel right' the next day. Two days later, he was taken to emergency room for **trouble breathing** and local reaction in left arm. Outcome of the events, seriousness and causality assessment was not reported.

PHHY2012US111763 (SR-HCP (HA)): An 11-years-old male subject with a history of peanut allergy, asthma and tree/mold allergy was vaccinated with Menveo and pneumococcal vaccine and diphtheria, tetanus, and acellular pertussis vaccine. Within minutes after vaccination, he experienced **shortness of breath**, wheezing and flushing. He was treated with epinephrine, prednisone, albuterol, and diphenhydramine hydrochloride. He was transported by ambulance to the emergency department. He also developed petechiae on upper body. The outcome of the events was reported as completely recovered. The reporter assessed the seriousness of the case as life-threatening. The causality of the events was not reported.

PHHY2013ES082017 (SR-Non-HCP (HA)): A 67 year old female subject with a history of small B-cell lymphoma (stage 1) was vaccinated with Menveo. On the same day of vaccination she presented with light pain and rash at injection point that improved the following day. Next day, she experienced pharyngeal hematoma and **tonsillitis** in left side with green mucus in nose and respiratory tract. She also had fever (36.7 and 36.4 degree Celsius) and light headache. Treatment medication included azithromycin. Health authority assessed the events as serious and suspected to Menveo. Outcome of the events pharyngeal hematoma, tonsillitis, fever and headache was reported as unknown.

PHHY2013FR089651 (SR-HCP (HA)): A 30-year-old male subject was vaccinated with Menveo, typhoid vaccine, and measles, mumps and rubella vaccine. On the same day, 20 minutes after vaccinations the subject presented with fever (39.3 degrees Celsius), polymyalgia and **dyspnea** and was hospitalized. The outcome of the events reported as recovered within 12 hours. The French health authority assessed the causal relationship between the adverse events and vaccines as possible.

PHHY2013GR135043 (SR-HCP): An 11-year-old male subject was vaccinated with Menveo. The next day, he experienced chest discomfort, **dyspnea** and chest pain. Later, in the afternoon when he started to exercise he again experienced the events. Clinical examinations conducted prior to vaccination were normal with exception of sphenoid chest (congenital birth defect). He underwent lab exams (liver and myocardial enzymes, stress test) which were normal. He did not receive any treatment for these events. The final outcome of the events was unknown. The physician reported that, the hospital register assessed the case as non-serious and causality to be unknown.

PHHY2013US044401 (SR-HCP (HA)): A 10-year-old female subject was vaccinated with Menveo. On the same day, she experienced tingling of extremities, fever within two hours after vaccination. Fever increased to 103.5 and continued the next day with **epistaxis** once and blood tinged phlegm. She also experienced weakness and felt some dizzy. The outcome of the events was reported as not recovered. The seriousness and causality of the events were not reported.

PHHY2014IT006939 (SR-HCP (HA)): A 16 year old female subject with no previous history of allergies and reactions to vaccinations had been presented with mild pharyngodinia without any fever at the recent anamnesis but the vaccination was not postponed. She was vaccinated with the first booster dose of Menveo along with the first booster dose of diphtheria, tetanus and pertussis vaccine. Following the vaccination, she experienced fever with a body temperature more than 39 degree Celsius, during the night of vaccination along with pharyngodinia. Three days later, she was treated with clarithromycin and amoxicillin and clavulanic acid thrice a day. But the antibiotic therapy did not help. She was hospitalized in infectious diseases department and the antibiotic treatment was suspended. Laboratory examinations only revealed moderate increase in CRP (C-reactive protein). The clinical finding corresponded to the defined syndrome of acute hyperpyrexia pharyngeal conjunctivitis (FAFC) due to adenovirus with the clinical triad of hyperpyrexia, pharyngitis and conjunctivitis. The conjunctivitis was, as usual, monolateral. The involvement of the lower respiratory airways was present with dry cough. She was discharged from the hospital after complete recovery. The reporter stated that the possibility of viral infection was supported by the concurrence of similar clinical picture in the contacts and that the correlation with the recent injection of Menveo appears purely temporal with the appearance of clinical symptoms without apparent causal connection. Health Authority assessed the events as serious and suspected the causality of the events to be related to the administration of the vaccines.

PHHY2014US000969 (SR-HCP (HA)): An 18-year-old female subject with medical history of asthma was vaccinated with Menveo. Five minutes after vaccination, she experienced syncope with **brief absence of respirations** and pulse. She visited the ER. She recovered during observation. The seriousness and causality were not reported.

3.18 Skin and subcutaneous tissue disorders

During this review period, a total of 219 adverse events from 149 case reports were identified under this body system. Of these, 33 were serious unlisted events. The serious unlisted events identified were blister, erythema, erythema multiforme, hyperhidrosis, leukocytoclastic vasculitis, palmar erythema, palpable purpura, petechiae, pruritus, purpura fulminans, rash, skin discoloration, skin warm, swelling face, and vascular purpura. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHY2012US099175 (SR-HCP (HA)): An 11 year old male subject was vaccinated with Menveo, diphtheria, pertussis, and tetanus vaccine and varicella vaccine. On an unspecified date the subject experienced warmth at both upper arms that night with large area of edema noted approximately three inches and began to experience smaller raised areas with **blister** like appearance on bilateral arms and legs, upper back and chest. Clear fluid noted at blister centers. The subject's mother gave diphenhydramine hydrochloride and avena sativa/melaleuca alternifolia oil. The subject had no fever but complained of nasal congestion only. The outcome and causality were not reported.

PHHY2012US111043 (SR-HCP (HA)): A 12 year old male subject was vaccinated with Menveo, human papilloma vaccine, hepatitis A vaccine and tetanus, diphtheria, and acellular pertussis. Two days after vaccination, in the emergency room he was diagnosed with fever, headache, body aches, **forehead swollen**, right arm, forearm and shoulder swollen. He was treated with steroids, antibiotics (unspecified) and diphenhydramine hydrochloride. The outcome of the events was recovered. Seriousness and causality assessment was not reported.

PHHY2013DE114262 (SR-HCP): An adult male subject was vaccinated for the first time with Menveo. Fourteen days after vaccination, he presented with exanthema multiforme. He was not hospitalized and only the skin was involved. The event outcome was reported as completely recovery after 4 weeks. The seriousness and causality of the event were not reported.

PHHY2013FR123883 (SR-HCP (HA)): A 24-year-old male subject with medical history of appendicular syndrome and skin eruptions due to ampicillin intake during childhood was vaccinated with Menveo and measles, mumps and rubella vaccine. Twenty days after vaccination, he was hospitalized due to vascular purpura of the lower limbs with polyarthralgia and orchitis which started around 15 days prior to hospitalization. Asthenia, rhinorrhea and purpuric lesion were noted at the thigh root and on the penis (associated with arthralgia and transient inflammatory swelling of the testicles). Cutaneous biopsy revealed a non-specific **leukocytoclastic vasculitis**. Immunofluorescence test showed vascular C3 complement deposit but no IgA immunoglobulins. Non-necrotizing, uninfected, vascular purpura of the lower limbs (drug-induced etiology) was diagnosed. He was treated symptomatically. Five days after onset, vascular purpura disappeared he was discharged from the hospital. Health authority assessed the causality as suspected to the vaccinations.

PHHY2013GR126122 (SR-HCP): An 11.5-year-old female subject was vaccinated with Menveo. On an unknown date after vaccination, she experienced rash on her upper and lower limbs. She visited a dermatologist who diagnosed **allergic rash** and hydroxyzine hydrochloride was administered as a treatment measure. The dermatologist did not think that the events were related to Menveo. She also visited the hospital (without being hospitalized) and cortisone was administered. Outcome was reported as improving. The physician assessed the reaction as medically significant. Neither the pediatrician nor the dermatologist assessed the events related to Menveo.

PHHY2013MY140894 (SR-HCP): A 39-year-old female subject was vaccinated with a dose of Menveo. On an unknown date after vaccination, she developed a **whole body rash** with body ache and muscle pain. She did not present with fever. The events resolved after treatment with antihistamine. The events were assessed as serious and suspected to administration of Menveo administration.

PHHY2013MY141122 (SR-HCP): A 56-year-old female subject was vaccinated with Menveo. On an unspecified date after vaccination, she experienced **whole body rash** with body ache and muscle pain. She was prescribed antihistamines (unspecified) and the symptoms resolved. The physician assessed the seriousness and causality as medically significant and suspected to the vaccination with Menveo.

PHHY2014US001265 (SR-HCP HA)): A 16-year-old male subject was vaccinated with Menveo, varicella virus vaccine, human papilloma vaccine, and diphtheria, pertussis, and

tetanus vaccine. One week after vaccination, he experienced several pin sized to quart size non-inflamed, no colored papules appeared on bilateral inner thighs and bilateral forearms. No treatment needed and events lasted for two days. She denied any other problems. The outcome of the events was reported as completely recovery. The seriousness and causality of the events were not reported.

3.19 Social circumstances

During this review period, there were no serious/unlisted events reported in this SOC.

3.20 Vascular disorders

During this review period, a total of 36 adverse events from 35 case reports were identified under this body system. Of these, 15 were serious unlisted events. The serious unlisted events identified were flushing, hemorrhage, hypotension, Kawasaki's disease, orthostatic hypotension, and pallor. Please note that this list of serious unlisted events may include listed events which were patterned under unlisted lead events and therefore took the listedness of the lead events; reference is made to the 'Tabulation by Body System of All Events Reported' for a complete listing of all reported events in Appendix 2. There were no reported fatal outcomes associated with this body system.

PHHO2010CR05755 (CT/HCP): A 10 week old male infant was vaccinated with MenACWY study vaccine. Twelve days after vaccination, the subject suffered from fever, irritability, abdominal pain and diarrhea. One day later, the subject underwent examinations and was diagnosed with **Kawasaki's disease**. During hospitalization, the subject received intravenous gammaglobulin. Following discharge, an echocardiogram performed, revealed dilation of the coronary artery. The subject was discharged with 150mg aspirin every 6 hours. An echocardiogram control was performed later which showed a decrease of the coronary artery dilation was observed. The subject's aspirin dose was changed from 150mg every 6 hours to 25 mg per day. The subject was in good clinical condition and was considered to have made a complete recovery from the event. The investigator reported that the possible relationship of the event with the study vaccination was due to temporality of the vaccine administration and the onset date of the event.

PHHO2010TW07994 (CT-HCP): A 12 week old female infant was vaccinated with MenACWY study vaccine. One month after vaccination, the subject developed poor controlled fever up to 39.8 degrees C, which persisted for five days. The next day she was hospitalized and was treated with ampicillin and gentamicin. Two days later she developed bilateral bulbar conjunctiva infection, oral mucous membrane changes, including red lips and strawberry tongue, palmar erythema, and skin rash over the face, trunk and four extremities. An echocardiogram showed negative findings. The subject was diagnosed with suspected **Kawasaki disease** and received treatment with intravenous immunoglobulin (IVIG) and high dose aspirin. The subject slowly recovered. The investigator suspected a causal relationship between the event and suspect vaccine.

PHHY2013CH111646 (SR-HCP (HA)): A female subject of an unknown age with no allergic reactions to food was vaccinated with Menveo. On the same date 20 hours after vaccination, she experienced **hypotension**, headache, vomiting and chills. Lab tests revealed arterial blood pressure to be 89/56 (units and normal range: not reported), pulse 45/min and

respiratory frequency to be 11/min. The subject recovered from the events 2 hours after the onset.

PHHY2013US084026 (SR-HCP (HA)): A 14-year-old male subject was vaccinated with Menveo. Right after vaccination he felt nauseous and appeared pale. He also complained of feeling dizzy and itchy rash on hands. He did not lose consciousness, had no drooling or wheezing. He received one epinephrine injection on his left thigh. The outcome of the events was reported as recovered. The case was reported as serious (life-threatening).

PHHY2013US127844 (SR-HCP (HA)): A 19-year-old male subject was vaccinated with Menveo. He fainted within minutes of vaccination and hit his head. He was bleeding and was taken to the emergency room of area hospital. He was treated and released. The outcome of the events was reported as complete recovery. The causality was not reported.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in VAERS forms in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA".

5 Estimate of patient exposure

During this review period from 19 Feb 2013 to 18 Feb 2014, (b) (4) doses of Menveo were sold in US.

6 Safety-related labeling changes and other regulatory actions taken since last report

During the reporting period, two lots of Menveo (Lot# M12118 and Lot# M12115) were recalled as a precautionary and voluntary action following an observation of higher-than-specified levels of residual moisture within the lyophilized Men A component vial of the mentioned lots. Changes to the label were made due to the approval of the Menveo Infant indication for 2-23 months of age.

There were no studies initiated or ongoing during the reporting period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

NOVARTIS

Novartis Vaccines and Diagnostics

Drug Safety and Epidemiology

Periodic Safety Report for the period 19-Feb-2014 – 18-Feb-2015

Menveo® [meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine]

BLA 125300

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1 Introduction

The Menveo® [meningococcal (groups A, C, Y and W-135) oligosaccharide diphtheria CRM_{197} conjugate vaccine] periodic safety report summarizes the post-marketing safety data for BLA 125300 received by Novartis Vaccines and Diagnostics (NVD) and processed by Drug Safety and Epidemiology of Novartis Pharma between 19-Feb-2014 and 18-Feb-2015.

Menveo is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135 and Y.

2 Summary of case reports

This analysis references the following attachments:

- Listings of all serious/unlabeled events (15-day alerts) submitted during the review period.

Table 2-1 15-Day Alerts

	Total initial reports submitted	Total follow-up reports submitted
Domestic	49	24
Foreign	47	62

- Listings and VAERs forms for all domestic serious/labeled events received during the review period.

Table 2-2 Serious/labeled Events

Total initial reports received	Total follow-up reports received
58	0

- Listings and VAERs forms for all domestic non-serious/unlabeled events received during the review period.

Table 2-3 Non-serious/unlabeled Events

Total initial reports received	Total follow-up reports received
645	09

- Listings only for all domestic non-serious/labeled events received during the review period.

Table 2-4 Non-serious/labeled Events

Total initial reports received	Total follow-up reports received
205	05

3 Review and analysis of 15-Day Alerts and other significant issues

A total of 182 initial and follow-up reports were received from US and non-US sources that were submitted to the Agency as 15-day alerts during the review period. Of these, 96 were initial reports and 86 were follow-up reports.

During this review period, there were no reports with a fatal outcome.

For the SOCs listed below, there were events report in these SOC during this review period, but they were neither serious/unlisted events nor reports with a fatal outcome:

- Ear and labyrinth disorders
- Metabolism and nutrition disorders
- Renal and urinary disorders

3.1 Blood and lymphatic system disorders

During this review period, a total of seven adverse events from seven case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were idiopathic thrombocytopenic purpura and lymphadenitis.

PHHO2014US000484 [Clinical Trial (CT), Healthcare Professional (HCP)]: A six-year-old female subject was enrolled in a phase 3b, randomized, observer-blind, placebo-controlled, multi-center study comparing immunogenicity, safety and one-year persistence of antibodies after either one or two doses of Novartis meningococcal ACWY conjugate vaccine, administered to healthy children two to 10 years of age. The subject's medical history included scleral hemorrhage, road traffic accident, asthma, contusion, petechie, and ecchymosis. Concomitant medications included budesonide and salbutamol. The subject was administered with the study vaccine (meningococcal ACWY vaccine Vs placebo; dose not reported) (total of two doses with the interval of two months) intramuscularly (IM). Sixty-six days after the second dose of vaccination, the child was taken to the hospital due to "easy bruising". Subsequently a week later, she had another fall from her bike leading to second episode of bruising and on the same day, her platelet count was low at 17,000/UL. The subject was treated with dexamethasone sodium phosphate for five days. A month later, marrow biopsy revealed typical but mild megakaryocyte hyperplasia without other cellular precursor abnormality. Approximately two months later, second marrow biopsy suggested "possibility" of immune thrombocytopenia with platelet count at 25,000/UL. The investigator confirmed the final diagnosis as **idiopathic thrombocytopenic purpura**. The outcome of the event was reported as condition improving. The investigator stated that the causal relationship between the event and the study vaccination was unknown, as the clinical history suggested a pre-study disorder but diagnostic confirmation was post-study and the insufficient information from the mother regarding the progression of disease contributes to this uncertainty.

PHHY2014US012801 [Spontaneous Report (SR), HCP]: This is a quality complaint report (reference number: 279242) as well. A 16-year-old male subject with unknown medical history was vaccinated with Menveo (batch: M12102, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect tetanus, diphtheria, and pertussis vaccine (other manufacturer, batch: 932Z9) and seasonal influenza vaccine (other manufacturer, batch: UH900AA). Concomitant medications were not reported. On an unknown date after vaccination, the subject developed vaccination site cellulitis, **lymphadenitis**, and pyrexia. The outcome of the events was reported as resolved and the causality was not reported. Based on the investigation performed, the quality assurance (QA) department stated that the Menveo vaccine (batch: M12102) was manufactured in accordance with the approved internal

procedures and it was in compliance with the current good manufacturing practices (cGMP) requirements.

3.2 Cardiac disorders

During this review period, a total of five adverse events from five case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were cyanosis, postural orthostatic tachycardia syndrome, and sinus tachycardia.

PHHY2014US170414 (SR, HCP): This is a quality complaint report (reference number: not available) as well. An 11-year-old female subject with unknown medical history was vaccinated with Menveo (batch: U4511AA and dose not reported) injection not otherwise specified (NOS). On the same day, the subject also was vaccinated with co-suspect human papilloma vaccine (other manufacturer, batch: J002641) and diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: N4352). Concomitant medication included amoxicillin. Thirty eight days after vaccinations, the subject developed **postural orthostatic tachycardia syndrome**, chronic fatigue syndrome, migraine, insomnia, syncope, serum ferritin decreased, vitamin D deficiency, abdominal pain, nausea, dizziness, and heart rate increased. She was consulted in the emergency room and was treated with iron supplements NOS, doxepin, sodium chloride (salt tablets), and fludrocortisone acetate. The outcome of the events was reported as condition unchanged and the causality was not reported. Based on the investigation performed, the QA department stated that, the Menveo vaccine (batch: U4511AA) was invalid, and therefore, no investigation would be performed for unknown batch number.

3.3 Endocrine disorders

During this review period, a total of three serious unlisted adverse events from one case report were identified under this body system. The serious unlisted events identified were Basedow's disease, hyperthyroidism, and myxedema.

PHEH2014US015504 (SR, HCP): This is a quality complaint report (reference number: 331430) as well. A 17-year-old female subject with medical history of hypersensitivity, thyroglossal cyst excision, oropharyngeal pain, and viral infection was vaccinated with a booster dose of Menveo (batch: M13064, dose not reported) injection NOS. Her previous vaccination (unspecified) was well tolerated. Concomitant medications were not reported. Approximately two weeks after vaccination, the subject developed dysstasia, coordination abnormal, muscular weakness, and fatigue. Subsequently on the next day, she also developed asthenia, myxedema, and **Basedow's disease**. Three weeks after vaccination, her skin was warm and dry with ecchymosis and she also developed edema, pain in extremity, and clonus (in lower extremities). Electrocardiogram was normal but she had mild sinus tachycardia. The etiology of all her symptoms was not clear. Her blood creatine phosphokinase was increased. Twenty three days after vaccination, the subject developed hyperthyroidism, paresis, and hypophosphatemia and MRI scan revealed radiculopathy. The subject stayed in hospital for two days and was discharged in stable condition with the prescription of thiamazole. The outcome of the events **Basedow's disease**, myxedema, and asthenia was reported as condition unchanged and not reported for other events. The causality of the events was not reported.

Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M13064) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

3.4 Eye disorders

During this review period, a total of 24 adverse events from 17 case reports were identified under this body system. Of these, seven were serious unlisted events. The serious unlisted events identified were diplopia, eye movement disorder, gaze palsy, photophobia, and strabismus.

PHHY2013IT074736 (HA, HCP): This case has been previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and this is an update. A 26-year-old female subject with unknown medical history was vaccinated with the booster injection of Menveo (batch: M12062 and dose not reported) IM. Concomitant medications were not reported. On the same day after vaccination, she developed pyrexia (39.8°C), vaccination site edema, headache, decreased appetite, abnormal dreams, **photophobia**, and vaccination site erythema. The outcome of the events was reported as resolved. The causality was reported as suspected to vaccination with Menveo. Based on the batch review performed, the QA department stated that the Menveo vaccine (batch: M12062) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

Follow-up information received during current review period did not include any medically significant information.

PHHY2014AR095624 (SR, HCP): This is a quality complaint report (reference number: 318080) as well. A seven-year-old female subject with unknown medical history was vaccinated with Menveo (batch: M13023, dose not reported) IM. Concomitant medications were not reported. On the same day after vaccination, the subject developed **gaze palsy** and presyncope (only fixating problem but not seizures). The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination with Menveo. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M13023) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2014GR143358 (SR, HCP): A 15-year-old female subject with unknown medical history was vaccinated with Menveo (batch number and dose not reported) injection NOS. Concomitant medications were not reported. On the next day after vaccination, the subject developed headache and vaccination site edema. On the fourth day after vaccination, she developed pyrexia (38°C), neck pain, and **photophobia**. Laboratory tests revealed erythrocyte sedimentation rate of 22 (unit not reported), white blood cells count of ‘8.500’ (unit not reported), and polymorphonuclear cells count of 76%. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination with Menveo.

PHHY2015GR012025 (SR, HCP): A 15-year-old male subject with unknown medical history was vaccinated with Menveo (batch: X13089/ A13089, dose not reported) injection NOS. The subject had no problems with previous vaccinations. On the next day after vaccination, the subject developed diplopia and **strabismus**. An unspecified period (“few

days") after vaccination, he also experienced photophobia. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination with Menveo.

3.5 Gastrointestinal disorders

During this review period, a total of 99 adverse events from 71 case reports were identified under this body system. Of these, 10 were serious unlisted events. The serious unlisted events identified were abdominal discomfort, abdominal pain, abdominal pain upper, mouth hemorrhage, nausea, swollen tongue, and vomiting.

PHEH2013US008408 (SR, HCP): This case has been previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and this is an update. This is a quality complaint report (reference number: 247963) as well. A 30-year-old polymedicated female subject with medical history of rubber sensitivity and drug hypersensitivity to promethazine was vaccinated with Menveo (batch: M11082, dose not reported) IM. On the same day after vaccination, she experienced sudden abdominal pain upper, nausea, fatigue, dizziness, and retching. Two hours later, she also experienced severe **vomiting** and diarrhea, subsequently she visited emergency room. She received treatment with intravenous sodium chloride, ondansetron hydrochloride, pantoprazole sodium sesquihydrate, ranitidine hydrochloride, prochlorperazine edisylate, chlorpromazine hydrochloride, diazepam, methylprednisolone sodium succinate, diphenhydramine in combination with paracetamol, and phenylpropanolamine hydrochloride. The outcome of the events was reported as resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch M11082) was manufactured in accordance with approved internal procedures and it was in compliance with the cGMP requirements.

Follow-up information received during current review period included update on the QA batch review report.

PHHY2014US012660 (SR, non-HCP): This is a quality complaint report (reference number: 279320) as well. An 11-year-old female subject with medical history of loose tooth was vaccinated with Menveo (batch: M13014, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect human papilloma vaccine (other manufacturer, batch: J011272), hepatitis A vaccine (other manufacturer, batch: 494G5), seasonal influenza vaccine (other manufacturer, batch: BJ2154), and diphtheria, tetanus, and acellular pertussis vaccine (other manufacturer, batch: B5X7M). Concomitant medications were not reported. On the next day after vaccinations, the subject was hospitalized due to **mouth hemorrhage**, petechie, contusion, platelet count decreased, and white blood cell count increased. Laboratory test revealed platelet count of 2000 (unit not reported), WBC count of 12.1 (unit not reported), hemoglobin level of 11.9 (unit not reported), and hematocrit level of 35.1 (unit not reported). The outcome of the events was reported as resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch M13014) was manufactured in accordance with approved internal procedures and it was in compliance with the cGMP requirements.

3.6 General disorders and administration sites conditions

During this review period, a total of 818 adverse events from 335 case reports were identified under this body system. Of these, 63 were serious unlisted events. The serious unlisted events identified were abasia, chest pain, chronic fatigue syndrome, extensive swelling of vaccinated limb, fatigue, feeling abnormal, gait disturbance, induration, inflammation, influenza like illness, local swelling, malaise, edema, edema peripheral, pain, performance status decreased, pyrexia, secretion discharge, swelling, tenderness, vaccination site erythema, vaccination site induration, vaccination site edema, vaccination site pain, vaccination site pruritus, vaccination site swelling, and vaccination site warmth.

Table 3-1 15-Day reports from the General disorders and administration sites conditions

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
HCP (n=12)							
PHEH2014US022974/ SR	18/ M	**Chest pain**/ Tremor/ Chills/ Pyrexia	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	Eight hours after vaccination, the subject developed **chest pain**, tremor, chills, and pyrexia. The outcome of the events was reported as condition unchanged. The causality of the events was not reported.
PHHY2013FR091981[#]/ HA	40/ M	**Drug ineffective**	Menveo (batch: not reported) SC	azathioprine/ prednisone/ tacrolimus	Renal transplant/ Hypertension/ Renal failure chronic	Not reported	The subject presented with seroconversion for only serogroup Y after one Menveo vaccination (**drug ineffective**). The HA assessed the causal relationship between the adverse event and Menveo as probable and as unlikely for tacrolimus, azathioprine, and prednisone. The French HA reported a drug interaction between tacrolimus, azathioprine and prednisone. It was reported that the vaccine was administered to an immunosuppressed subject and that he received vaccine subcutaneously (off-label administration). Since the batch number was not reported, a batch specific review was not performed. However, product investigation from the QA department did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
PHHY2013KR130323#/ SR	12/ M	**Extensive swelling of vaccinated limb**/ Wrong technique in drug usage process	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	After vaccine mix, the used needle should be replaced with a new one for injection, but to this subject the injection was done without replacement of used needle (wrong technique in drug usage process). On the third day after vaccination, he experienced **extensive swelling of vaccinated limb** which persisted for two days. The outcome of the event extensive swelling of vaccinated limb was reported as resolved. The causality was reported as suspected to the vaccination with Menveo. The APR report of the Menveo vaccine did not find any abnormality.
PHHY2013US110851#/ SR	16/ F	**Feeling abnormal**/ Face edema/ Pharyngeal edema/ Oropharyngeal pain/ Blood creatinine increased	Menveo (batch: M11051) IM	human papilloma vaccine (other manufacturer, H016238), inactivated polio vaccine (other manufacturer, batch: H13541)	Renal transplant/ Food allergy	azathioprine/ cholecalciferol/ clindamycin/ sodium bicarbonate/ calcium carbonate/ tacrolimus prednisone	On the second day after vaccination, the subject was **feeling abnormal** (“weird”) and developed face edema, pharyngeal edema, oropharyngeal pain, and her blood creatinine increased. The outcome of the events was reported as resolved. The causality of the events was not assessed. Batch review was performed and it did not find any abnormality.
PHHY2014AR030504/ SR	Six months/ Unk	**Vaccination site erythema**/ Vaccination site induration/ Pyrexia/ Swelling	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	On an unknown date after vaccination, the subject presented with **erythema** and induration at the vaccination site followed by pyrexia. The subject also experienced swelling (unspecified site). The outcome of the events pyrexia and swelling was reported as resolved and not reported for other events. The causality of the events was not reported.
PHHY2014BD042886/ SR	Three/ M	**Vaccination site erythema**/ Vaccination site swelling	Menveo (batch: not reported) injection NOS	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **erythema** and swelling at the vaccination site. The outcome and causality of the events were not reported.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
PHHY2014ES085270/ SR	46/ F	**Asthenia**/ Myalgia/ Arthralgia	Menveo (batch: A90CA041B) injection NOS	Not reported	Not reported	Not reported	Four hours after vaccination, the subject developed **asthenia**, myalgia, and arthralgia. The outcome of the event was reported as condition unchanged. The causality was reported as suspected to the vaccination with Menveo.
PHHY2014GR065118#/ SR	Eight/ F	**Local swelling**/ Burning sensation/ Erythema	Menveo (batch: M13089) injection NOS	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **local swelling**, burning sensation, and erythema. The outcome of the events was reported as resolved. The causality of the event was reported as suspected to vaccination with Menveo. Batch review was performed and it did not find any abnormality.
PHHY2014GR065119#/ SR	Four/ M	**Local swelling**/ Burning sensation/ Erythema	Menveo (batch: A13089) injection NOS	Not reported	Not reported	Not reported	On the same day few hours after vaccination, the subject developed **local swelling**. Eight hours after vaccination, he also developed burning sensation and erythema. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination with Menveo.
PHHY2014GR075749/ SR	Two/ F	**Inflammation**/ edema peripheral/ C-reactive protein increased/ Balance disorder/ Rash	Menveo (batch: not reported) injection NOS	Not reported	Not reported	Not reported	On the second day after vaccination, the subject developed **inflammation**, edema peripheral, C-reactive protein increased, balance disorder, and rash. The outcome of the events was reported as resolved. The causality of the events inflammation, edema peripheral, C-reactive protein increased and rash was reported as suspected and not reported for the event balance disorder.
PHHY2014GR126822#/ SR	13/ F	**Pyrexia**/ Vaccination site edema/ Vaccination site pain	Menveo (batch: M13089) injection NOS	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed edema and pain at the vaccination site. On the second day after vaccination, she also developed **pyrexia**. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
							with Menveo.
PHHY2014US068695/ Lit	Five/ F	**Edema peripheral**/ Local swelling/ Headache/ Neck pain/ Pain in extremity/ Pyrexia/ Nausea/ Erythema	meningococcal vaccine INN (batch: not reported) injection NOS	pneumococcal vaccine (other manufacturer, batch: not reported)	Otitis media/ Urticaria/ Arthropod bite/ Headache/ Ear tube insertion/ Asthma/ Pain in extremity/ Splenomegaly/ Mycotic allergy/ Hemoglobin C disease/ House dust allergy/ vaccination history of pneumococcal vaccine, meningococcal vaccine, hepatitis B vaccine, and annual influenza vaccines	Not reported	On the next day (early morning) after the vaccination, she developed headache, neck pain, and pain in extremity with pyrexia (102.9°F). She was presented to the hospital with **edema peripheral**, local swelling, and nausea. She was discharged with morphine and ibuprofen. The outcome of the events edema peripheral and peripheral swelling was resolved and not reported for other events. The author concluded that since the swelling occurred in the same arm as the previous pneumococcal vaccination and as it was a second dose of pneumococcal vaccine, it was likely that pneumococcal vaccine caused the adverse event. Additionally, the immune reaction might have been amplified by the conjugated meningococcal vaccine administered concurrently in the other arm. Finally the pain that occurred before and during the edema peripheral and peripheral swelling might have been at least partially related to sickle cell vaso-occlusion.

SR=Spontaneous Report; HCP=Healthcare Professional; Lit=Literature; Unk=Unknown; M=Male; F=Female; PT=Preferred Term; HA=Health Authority; NOS=Not Otherwise Specified; IM=Intramuscular; SC=Subcutaneous; APR=Annual Product Review; QA=Quality Assurance; *the case was previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and the follow-up was received during the current review period; #Quality complaint report; ^Historical condition/ Current condition/ Procedure/ Historical drug; Primary events of the System Organ Class are bold

3.7 Hepatobiliary disorders

During this review period, one serious unlisted adverse event from one case report was identified under this body system. The serious unlisted event identified was jaundice.

PHHY2014US132725 (SR, HCP): This is a quality complaint report (reference number: not reported) as well. A 19-year-old female subject with medical history of developmental delay and depression was vaccinated with Menveo (batch: A13001, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect human papilloma vaccine (other manufacturer, batch: K001502) and diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: A54AL). Concomitant medication included fluoxetine. On the third day after vaccinations, the subject developed **jaundice**, abdominal pain, and her transaminases increased. The subject was sent to an emergency room. The outcome of the events was reported as resolved and the causality was not reported. Upon the follow-up, the QA department stated that the Menveo vaccine (batch: A13001) was not a valid batch number; hence QA investigation would not be performed.

3.8 Immune system disorders

During this review period, a total of 15 adverse events from 15 case reports were identified under this body system. Of these, one was a serious unlisted event. The serious unlisted event identified was serum sickness.

PHEH2014US012139 (SR, HCP): A 13-year-old male subject with unknown medical history was vaccinated with Men A lyophilized conjugate component of Menveo (batch: A12129 and dose not reported) reconstituted with a sterile water instead of MenCYW-135 liquid component (wrong technique in drug usage process) IM. On the same day, the subject was also vaccinated with co-suspect diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: 52DMS). Concomitant medications were not reported. On the same day after vaccination, the subject developed rash, dyspnea, and **hypersensitivity**. The subject was treated with corticosteroids NOS. The outcome of the events was reported as resolved. The causality was not explicitly reported; however, it was reported that the subject also administered other unspecified medications around the same time as Menveo, which could have caused the allergic reaction.

PHFR2014GB002185 (SR, non-HCP): A six-year-old female subject with medical history of thalassemia beta was vaccinated with Menveo INN (unknown manufacturer, batch and dose: not reported) injection NOS. Concomitant medications were not reported. On an unknown date after vaccination, she experienced **hypersensitivity** and was taken to hospital for treatment (details unspecified). The outcome of the event was not reported.

PHHY2014BR125679 (SR, HCP): A five-year-old female subject with medical history of dermatitis atopic was vaccinated with Menveo (batch: M14048, dose not reported) IM. Thirty-six hours after vaccination, the subject developed **hypersensitivity**, urticaria, and rash generalized. The subject was treated with dexchlorpheniramine and dexamethasone, and the events resolved. The causality of the events was reported as suspected to the vaccination with Menveo.

PHHY2014KR067508 (SR, HCP): A three-year-old female subject with unknown medical history was vaccinated with Menveo (batch: M13045) 0.5 mL IM. Concomitant medications were not reported. On the next day after vaccination, the subject developed **hypersensitivity**, pruritus, extensive swelling of vaccinated limb, and erythema. The subject was treated with antibiotics and antihistamines NOS and the events resolved. The causality of the events was reported as suspected to the vaccination with Menveo.

PHHY2014KR093604 (SR, HCP): A two-year-old female subject with medical history of cerebral palsy and cortical dysplasia was vaccinated with Menveo (batch: X13101) 0.5 mL IM. Concomitant medications were not reported. On the same day after vaccination, the subject experienced dyspnea, wheezing, vaccination site rash, localized edema, urticaria, and **anaphylactic reaction**. The subject was treated with dexamethasone, epinephrine, budesonide, and guaifenesin with combination of salbutamol sulfate. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to the vaccination with Menveo.

PHHY2014KR121072 (SR, HCP): A two-year-old female subject with medical history of treatment with anti-allergic agents and familial history of hypersensitivity was vaccinated with Menveo (batch: M12066) 0.5 mL IM. Concomitant medications included unspecified non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. On the same day one hour after vaccination, the subject was hospitalized due to urticaria, dyspnea, and pyrexia (38.5°C). She also developed flushing, cough, wheezing, and pruritus generalized along with rash generalized. The subject was treated with epinephrine, antihistamines NOS, oxygen therapy, intravenous corticosteroids NOS, and intravenous fluids for the events. The final diagnosis was noted as **anaphylactic reaction**. The subject was discharged after two days. The outcome of the events pruritus generalized, rash generalized, flushing, cough, and wheezing was reported as condition improving and resolved for the other events. The causality of the events was reported as suspected to the vaccination with Menveo.

PHHY2014KR146014 (SR, HCP): A three-year-old female subject with unknown medical history was vaccinated with Menveo (batch: M13043) 0.5 mL IM. Concomitant medications were not reported. On the same day after vaccination, she developed **hypersensitivity**, angioedema, face edema, induration, and erythema. The subject was taken to hospital and treated with prednisolone, dexamethasone, pheniramine, piprinhydrinate, ambroxol hydrochloride, tulobuterol hydrochloride, *Bacillus subtilis* in combination with *Enterococcus faecalis*, codeine in combination with phenobarbital, and amoxicillin sodium in combination with clavulanate potassium. After one hour of onset, no other symptom occurred and the subject went home (not hospitalized). The outcome of the events was not reported and the causality was not reported.

PHHY2014US027656 (SR, HCP): This is a quality complaint report (reference number: 287524) as well. A 13-year-old female subject with unknown medical history was vaccinated with Menveo (batch: A12122, dose not reported) injection NOS. On the same day, the subject was also vaccinated with co-suspect human papilloma vaccine (other manufacturer, batch: J006850), hepatitis A vaccine (other manufacturer, batch: JR737), hepatitis B vaccine (other manufacturer, batch: AHBVC253BA), influenza vaccine (other manufacturer, batch: 59YY4), and diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: AC52B097BA). Concomitant medications were not reported. On the third day after vaccination, the subject

developed **serum sickness**. The outcome of the event was reported as condition unchanged and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: A12122) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

3.9 Infections and infestations

During this review period, a total of 52 adverse events from 45 case reports were identified under this body system. Of these, 40 were serious unlisted events. The serious unlisted events identified were abscess, cellulitis, *Enterovirus* infection, mastoiditis, meningitis aseptic, meningitis meningococcal, meningitis viral, meningococcal sepsis, nasopharyngitis, pneumonia mycoplasmal, sinusitis, staphylococcal infection, vaccination site abscess, vaccination site cellulitis, vaccination site infection, and vaccination site pustule.

Table 3-2 15-Day reports from the Infections and infestations

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
HCP (n=33)							
PHEH2012US016438[#]/ SR	11/ F	**Nasopharyngitis**/ Oropharyngeal pain/ Cough/ Disorientation/ Dizziness/ Nausea/ Pyrexia/ Vaccination site erythema/ Vaccination site pain/ Vaccination site swelling/ Vaccination site rash/ Decreased appetite	Menveo (batch: M11075) IM	Not reported	Not reported	varicella virus vaccine/ diphtheria, tetanus, and acellular pertussis	On the third day after vaccination, she developed vaccination site erythema, vaccination site pain, and vaccination site swelling. On the sixth day after vaccination, she developed oropharyngeal pain, cough, disorientation, dizziness, nausea, pyrexia (104°F), and she had decreased appetite. Subsequently four days later, she experienced **nasopharyngitis**. On an unknown date, the subject also developed vaccination site rash. On an unspecified date, she was hospitalized. The outcome of the events was resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH2013US016359[#]/ SR	13/ M	**Cellulitis**/ Erythema/ Tenderness/ Vaccination site warmth/ Extensive swelling of vaccinated limb	Menveo (batch: M12123) IM	Not reported	Not reported	Not reported	On the same day two hours after vaccination, the subject developed erythema, tenderness, vaccination site warmth, and extensive swelling of vaccinated limb. On an unspecified date after vaccination, he was diagnosed with **cellulitis**. The outcome of the events was reported as resolved. The causality of the event cellulitis was reported as related to vaccination with Menveo. Batch review was performed and it did not find any abnormality.
PHEH2013US021639[#]/ SR	11/ M	**Vaccination site cellulitis**/ Skin warm/ Erythema/ Skin discoloration/ Incorrect storage of drug	Menveo (batch: A1105) 0.5 mL IM	Not reported	Not reported	Not reported	Before vaccination, Menveo vials had “reached 32°F on two occasions” (incorrect storage of drug). On an unknown date after vaccination, the subject developed **vaccination site cellulitis**, skin warm, erythema, and skin discoloration. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
PHEH20 14US011 474#/ SR	12/ M	**Cellulitis**/ Skin warm/ Abscess/ Incorrect route of drug administration	Menveo (batch: M13017) 0.5 mL SC	Not reported	Not reported	Not reported	The subject administered Menveo subcutaneously (incorrect route of drug administration). On the second day after vaccination, he developed **cellulitis**. Subsequently on the next day, he also developed abscess and his skin was warm. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH20 14US011 475#/ SR	16/ F	**Cellulitis**/ Incorrect route of drug administration	Menveo (batch: M12104) 0.5 mL SC	Not reported	Not reported	Not reported	The subject administered Menveo subcutaneously (incorrect route of drug administration). On the next day after vaccination the subject developed **cellulitis**. The outcome of the event was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH20 14US012 397#/ SR	Unk/ M	**Vaccination site cellulitis**	Menveo (batch: M13012) 0.5 mL IM	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **vaccination site cellulitis**. The outcome of the event was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH20 14US012 586#/ SR	Unk/ F	**Vaccination site cellulitis**	Menveo (batch: M13012) 0.5 mL IM	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **vaccination site cellulitis**. The outcome of the event was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH20 14US015 281#/ SR	Unk/ Unk	**Cellulitis**	Menveo (batch: not reported) IM	diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: not reported)	Not reported	Not reported	Both the vaccines were received on the same day. On an unknown date after vaccinations, the subject developed **cellulitis**. The outcome and causality of the event was not reported. Batch review was performed and it did not find any abnormality.
PHFR201 4GB0083	47/ M	**Cellulitis**/ Pain in extremity/	Menveo (batch:	Not reported	Not reported	Not reported	On an unknown date, after vaccination the subject developed pain in extremity. Four to five days after

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
16[#]/ SR		Inflammation/ Erythema/ Rash	M13097) injection NOS				vaccination, he developed **cellulitis**, inflammation, erythema, and rash. The outcome of the events was reported as condition unchanged. The causality of the events was not reported. Batch review was performed and it did not find any abnormality.
PHFR2014GB00895[#]/ SR	20/ F	**Meningitis meningococcal**/ Vaccination failure	Menveo (batch: not reported) injection NOS	Bexsero® (meningococcal B vaccine) (batch: not reported) injection NOS	Hemolytic uremic syndrome	eculizumab	Both the vaccines were received on the same day. Forty eight days later, the subject was administered with another dose of Bexsero. Eight months after the Menveo vaccination, the subject developed **meningitis meningococcal** (vaccination failure). The outcome and causality of the events were not reported. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2013AR119138[#]/ SR	Four/ F	**Vaccination site cellulitis**/ Vaccination site edema/ Vaccination site induration/ Injection site discoloration/ pyrexia	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	Eight hours after vaccination, she developed vaccination site edema and pyrexia (39°C). On the next day, she was hospitalized due to due to persistent pyrexia and vaccination site induration. On the second day after vaccination, the child also developed **vaccination site cellulitis** and injection site discoloration. The child was discharged after two days of hospitalization. The outcome of the event vaccination site induration was reported as resolved; not reported for injection site discoloration; and condition improving for the other events. The causality was not reported. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2013BE082220[#]/ SR	19/ F	**Meningitis aseptic**/ Meningism/	Menveo (batch: M11021)	Not reported	Protein C deficiency/ Meningitis	meningococcal C vaccine	Both the vaccines were received on the same day. An unspecified period after vaccinations, the subject was hospitalized due to **meningitis**

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		Pyrexia/ CSF white blood cell count decreased	injection NOS				**aseptic**, meningism, pyrexia, and CSF white blood cell count decreased. The outcome of the events was reported as resolved. The reporter did not suspect Menveo or meningococcal C vaccine to cause these recurring episodes of meningitis either by lack of efficacy or as an adverse reaction. Based on the review of the APR reports, the QA department did not find any abnormality.
PHHY2013BR082627[#]/ SR	47/ F	**Vaccination site infection**/ Migraine/ edema/ Vaccination site pain/ Vaccination site erythema/ Pain/ Pyrexia	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	On the same day night after vaccination, the subject developed vaccination site pain, edema, migraine, pain, pyrexia, and vaccination site erythema. On an unknown date, she also developed **vaccination site infection**. The outcome of the event pyrexia was reported as resolved and not reported for the other events. The causality was not reported. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2013BR083257[#]/ SR	10/ M	**Cellulitis**/ Extensive swelling of vaccinated limb/ Skin warm/ Induration/ Erythema/ Pyrexia	Menveo (batch: not reported) IM	Not reported	None	Not reported	Six hours after vaccination, The subject developed extensive swelling of vaccinated limb, skin warm, induration, erythema, and pyrexia. He consulted with physician and was diagnosed with **cellulitis**, eight hours after vaccination. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to vaccination with Menveo. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2014DE143370[#]/ HA	12/ F	**Cellulitis**/ Vaccination site swelling/ Vaccination site erythema/	Menveo (batch: M13021) IM	Not reported	Not reported	Not reported	One to two days after vaccination, the subject developed swelling, erythema, warmth, and vesicles at the vaccination site, and **cellulitis**. She was hospitalized due to the events. The outcome of the events was reported as condition unchanged.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		Vaccination site warmth/ Vaccination site vesicles					The causality of the events was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014GR118762# / SR	12/ M	**Cellulitis**/ Extensive swelling of vaccinated limb/ Vaccination site edema/ Vaccination site pain/ Vaccination site erythema/ Vaccination site pruritus/ White blood cell count increased/ Staphylococcal infection	Menveo (batch: not reported) injection NOS	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **cellulitis**, extensive swelling of vaccinated limb, vaccination site edema, vaccination site pain, vaccination site erythema, vaccination site pruritus, white blood cell count increased, and staphylococcal infection. The subject was hospitalized for two days due to the events. The outcome of the events was reported as resolved. The causality of the events was suspected to vaccination with Menveo. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2014IT095167# / SR	Unk/ F	**Meningococcal sepsis**/ Vaccination failure	Menveo (batch: not reported) injection NOS	Menjugate® (meningococcal C vaccine) (batch: not reported) injection NOS	Not reported	eculizumab	On an unknown date the subject received co-suspect Menjugate vaccine. Approximately three to four months after vaccination with Menveo, the subject presented with **meningococcal sepsis** (vaccination failure). The outcome and causality of the events were not reported. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2014PH137531# / SR	Seven/ M	**Cellulitis**/ Extensive swelling of vaccinated limb/ Pyrexia	Menveo (batch: M13029) injection NOS	Not reported	Hypersensitivity/ Asthma	Not reported	On the second day after vaccination, the subject developed extensive swelling of vaccinated limb and pyrexia. Subsequently on the next day, he developed **cellulitis**. The outcome of the events was reported as unknown. The causality of the events suspected to vaccination with Menveo. Batch review was performed and it did not find any

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
							abnormality.
PHHY2014US006380[#]/ SR	11/ F	**Pneumonia mycoplasmal**/ Malaise/ Joint instability/ Dysstasia/ Abasia/ Influenza like illness/ Headache/ Arthralgia/ Back pain/ Amnesia/ Disturbance in attention	Menveo (batch: not reported) injection NOS	pneumococcal vaccine (other manufacturer, batch: F75398)	Walking aid user/ Activities of daily living impaired/ Wheelchair user	Not reported	Both vaccines were received on the same day. On the same day after vaccinations, she experienced influenza like illness and headache with no fever for three days. Subsequently, one month later she developed joint instability, back pain, and arthralgia. She also developed abasia and dysstasia; she was hospitalized for four days. On an unknown date, she developed **pneumonia mycoplasmal** and was treated with azithromycin. Two weeks later she went back to hospital for a headache which lasted for six days. She also developed disturbance in attention, amnesia, and malaise. The outcome of the events was reported as condition unchanged. The causality of the events was not reported. The initially reported batch 024011 was not a valid Menveo batch number and hence the QA investigation would not be performed.
PHHY2014US012854[#]/ SR	55/ F	**Cellulitis**/ Erythema/ Local swelling	Menveo (batch: not reported) IM	Not reported	Not reported	metformin/ olmesartan medoxomil	On the fourth day after vaccination, the subject developed **cellulitis**, erythema, and peripheral swelling and was hospitalized for three days. The outcome of the events was reported as condition unchanged. The causality was not reported. Since the batch number was not reported, a batch specific review did not perform. However, product investigation from the QA department did not find any abnormality.
PHHY2014US047023[#]/ SR	11/ F	**Vaccination site cellulitis**/ Vaccination site erythema/ Vaccination site pruritus/ Vaccination site	Menveo (batch: AX13012) IM	hepatitis A vaccine (other manufacturer, batch: 99P59)/ human papilloma vaccine (other manufacturer,	Not reported	Not reported	All the vaccines were received on the same day. On an unknown date after vaccinations, the subject developed **cellulitis**, erythema, pruritus, edema, and abscess at the vaccination site. The outcome of the events was reported as unknown and the causality was not reported. Batch review was performed and it did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		edema/ Vaccination site abscess		batch: J006850)/ Influenza virus vaccine (other manufacturer, batch: UH921AA)			
PHHY2014US070875#/ SR	11/ M	**Vaccination site cellulitis**/ Vaccination site erythema/ Vaccination site swelling	Menveo (batch: M13012) IM	human papilloma vaccine (other manufacturer, batch: J012438)/ diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: 253B4)	Seasonal allergy	loratadine	All the vaccines were received on the same day. On the third day after vaccinations, the subject developed **cellulitis**, erythema, and swelling at the vaccination site. The outcome of the events was reported as condition unchanged and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US092323#/ SR	13/ F	**Cellulitis**/ Nausea/ Headache/ Vaccination site pain/ Vaccination site erythema/ Vaccination site swelling/ Vaccination site induration/ Vaccination site warmth	Menveo (batch: M13058) IM	human papilloma vaccine (other manufacturer, batch: J012212)	Not reported	Not reported	Both the vaccines were received on the same day. On the second day after vaccinations, the subject developed pain, erythema, swelling, induration, and warmth at the vaccination site. On the same day, the subject also developed **cellulitis**, nausea, and headache. The outcome of the events was reported as unknown and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US098896#/ SR	10/ F	**Cellulitis**/ Tenderness/ Erythema/ Pruritus/ Vaccination site induration	Menveo (batch: M13046) IM	human papilloma vaccine (other manufacturer, batch: J012435)/ diphtheria, pertussis, and tetanus vaccine (other	Not reported	paracetamol/ diphenhydramine hydrochloride/ cefalexin	All the vaccines were received on the same day. On the third day after vaccinations, the subject developed **cellulitis**, tenderness, erythema, pruritus, and vaccination site induration. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
				manufacturer, batch: N435Z)			
PHHY2014US112197# / SR	42/ F	**Vaccination site cellulitis**/ Vaccination site swelling/ Vaccination site pain/ Vaccination site erythema	Menveo (batch: A13014) IM	measles, mumps, and rubella vaccine (other manufacturer, batch: H020255)	Not reported	Not reported	Both the vaccines were received on the same day. On the next day after vaccinations, the subject developed **cellulitis**, swelling, pain, and erythema at the vaccination site. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US112261# / SR	11/ M	**Cellulitis**/ Erythema/ Local swelling/ Tenderness	Menveo (batch: M13064) IM	human papilloma vaccine (other manufacturer, batch: J015378)/ diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: 17J44)	Not reported	Not reported	Both the vaccines were received on the same day. On the third day after vaccinations, the subject developed **cellulitis**, erythema, peripheral swelling, and tenderness. The outcome of the events was reported as unknown and the causality of the events was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US112308# / SR	10/ M	**Cellulitis**/ Secretion discharge/ Erythema/ Extensive swelling of vaccinated limb/ Skin warm/ Induration	Menveo (batch: M12124) IM	diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: N2K27)	Allergy to animal/ Drug hypersensitivity	Not reported	Both the vaccines were received on the same day. On the second day after vaccinations, the subject developed **cellulitis**, secretion discharge, erythema, and extensive swelling of vaccinated limb. Subsequently on the next day, he also developed induration and his skin was warm. The outcome of the events was reported as unknown and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US112520# / SR	14/ F	**Cellulitis**/ Swollen tongue/ Swelling face/ Local swelling/ Pain/ Vaccination site swelling/ Extensive swelling	Menveo (batch: M13030) injection NOS	Not reported	Not reported	Not reported	On the second day after vaccination, the subject developed **cellulitis**, swollen tongue, swelling face, local swelling, pain, vaccination site swelling, and extensive swelling of vaccinated limb. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		of vaccinated limb					
PHHY2014US148675#/ SR	12/ M	**Cellulitis**/ Injection site swelling	Menveo (batch: M13053) IM	diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: C4506AC)	Not reported	Not reported	Both the vaccines were received on the same day. On the third day the subject developed **cellulitis** and injection site swelling. The outcome of the events was reported as unknown and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US148797#/ SR	11/ M	**Cellulitis**/ Skin warm/ Swelling/ Erythema	Menveo (batch: M14023) IM	human papilloma vaccine (other manufacturer, batch: J009788)/ diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: L7J44)	Not reported	diphenhydramine hydrochloride	All the vaccines were received on the same day. On the second day after vaccinations, the subject developed **cellulitis**, skin warm, swelling, and erythema. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US149776#/ SR	11/ F	**Vaccination site cellulitis**/ Vaccination site pain/ Vaccination site erythema/ Vaccination site warmth	Menveo (batch: M13014) IM	human papilloma vaccine (other manufacturer, batch: K001500) / diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: XP4D)	Not reported	Not reported	All the vaccines were received on the same day. On the next day after vaccinations, the subject developed **cellulitis**, pain, erythema, and warmth at the vaccination site. The outcome of the events was reported as resolved and the causality was reported. Batch review was performed and it did not find any abnormality.
PHHY2014US170081#/ SR	11/ M	**Vaccination site cellulitis**	Menveo (batch: M14023) injection NOS	human papilloma vaccine (other manufacturer, batch: J015378)/ seasonal influenza vaccine (other manufacturer,	Rhinitis allergic/ Asthma/ Treatment with pseudoephedrine hydrochloride	Not reported	All the vaccines were received on the same day. On the same day after vaccinations, the subject developed **vaccination site cellulitis**. The outcome of the event was reported as unknown and the causality was not reported. Batch review was performed and it did not find any abnormality.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
				batch: LZ4S2)/ diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: N3BE2)			
PHHY2015BR001278#/ SR	Three/ F	**Vaccination site cellulitis**/ Pyrexia/ Vaccination site pustule/ Vaccination site erythema/ Vaccination site edema	Menveo (batch: M14051/ ZC236) IM	Not reported	Not reported	Not reported	On the same day (night) after vaccination, the subject developed pyrexia, vaccination site pustule, vaccination site erythema, and vaccination site edema. On the third day after vaccination, the child also developed **vaccination site cellulitis**. The outcome of the events was reported as resolved. The causality of the events was suspected to vaccination with Menveo. Batch review was performed and it did not find any abnormality.
Non-HCP (n=02)							
PHHY2014GR088567#/ SR	12/ M	***Enterovirus* infection**/ Meningitis viral	Menveo (batch: M13089) injection NOS	Not reported	Diabetes mellitus	Not reported	On the third day after vaccination, the subject presented with symptoms of viral meningitis. Subsequently two days later, he was hospitalized and diagnosed with meningitis. During hospitalization, laboratory test revealed ***Enterovirus* infection**. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014IT159026#/ SR	18/ F	**Meningococcal sepsis**/ Vaccination failure	Menveo (batch: not reported) injection NOS	eculizumab	Not reported	Not reported	An unspecified period after vaccination, the subject developed **meningococcal sepsis** and vaccination failure. The outcome and causality of the events were not reported. Since the batch number was not reported, a batch specific review was not performed. However, product investigation from the QA department did not find any abnormality.

SR=Spontaneous Report; HCP=Healthcare Professional; Unk=Unknown; M=Male; F=Female; PT=Preferred Term; HA=Health Authority; NOS=Not Otherwise Specified; IM=Intramuscular; SC=Subcutaneous; APR=Annual Product Review; QA=Quality Assurance; *the case was previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and the follow-up was received during the current review period; #Quality complaint report; ^Historical condition/ Current condition/ Procedure/ Historical drug; Primary events of the System Organ Class are bold

3.10 Injury, poisoning and procedural complications

During this review period, a total of 585 adverse events from 576 case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were contusion, road traffic accident, and vaccination failure.

PHHY2014CA145966 (SR, non-HCP): A 62-year-old female subject with unknown medical history was vaccinated with Menveo (batch: not reported, dose not reported) injection NOS. Co-suspect medication included metoprolol tartrate for hypertension, doxazosin mesylate, and hydralazine hydrochloride. Concomitant medications were not reported. Approximately six months after vaccination, the subject experienced **road traffic accident**. After her physical examination, she was discharged from hospital within less than three hours. In the first half of the same month after accident, she experienced cough and also had increased bronchial secretion which were treated with moxifloxacin. Approximately eight months after vaccination, her medications were altered due to hypertension. The dose of metoprolol was increased to 175 mg two times a day. After unspecified days of vaccination, the dose of co-suspect doxazosin mesylate was increased to 16 mg and the co-suspect hydralazine hydrochloride was also ongoing. Approximately eight and a half months after vaccination, she again developed cough and seven days later she had increased bronchial secretion. Subsequently few days later, she developed bronchitis and her body temperature increased (38.5°C). The subject was treated with amoxicillin and paracetamol. The outcome of the event body temperature increased was resolved; condition improving for bronchitis; and not reported for the other events. The causality of the events was not reported.

3.11 Investigations

During this review period, a total of 41 adverse events from 29 case reports were identified under this body system. Of these, 20 were serious unlisted events. The serious unlisted events identified were blood creatine phosphokinase increased, blood creatinine increased, C-reactive protein increased, CSF pressure decreased, CSF protein increased, CSF white blood cell count decreased, CSF white blood cell count increased, hemoglobin decreased, heart rate increased, nuclear magnetic resonance imaging abnormal, platelet count decreased, serum ferritin decreased, transaminases increased, vitamin D decreased, and white blood cell count increased.

PHHY2014CA130141 (SR, non-HCP) A 57-year-old female subject with unknown medical history was vaccinated with Menveo (batch number and dose not reported) IM. Two months later the subject was vaccinated with co-suspect Bexsero (batch: not reported) 0.5 mL IM and another dose of Bexsero (batch: not reported) within a three month interval. Concomitant medications were not reported. In the same month after vaccination with Bexsero, she experienced hyperesthesia. In the third month after vaccination with Menveo (next month after vaccination with Bexsero), she had intermittent headaches which was treated with paracetamol. In the same month, she also experienced two episodes of diarrhea. In the next month, her **blood creatinine increased** to 400 (unit not reported). In the subsequent month, her blood creatinine further increased to 451 (unit not reported) and experienced dizziness and toothache (two molar). She underwent tooth extraction. In the same month, the subject developed nail bed bleeding (index finger). On an unknown date, the subject also developed

fatigue and somnolence. The outcome of dizziness and headache was reported as resolved and not reported for the other events. The causality of the events was not reported.

PHHY2014CA159906 (SR, non-HCP): A 25-year-old male subject with unknown medical history was vaccinated with Menveo (batch number and dose not reported) IM. Concomitant medications were not reported. Approximately one year and eight months after vaccination, the subject's **hemoglobin decreased** to 85 (unit not reported), which was managed with one blood transfusion. On an unknown date, his blood iron increased. The subject was treated with deferasirox. The outcome of the events was not reported.

PHHY2014DE085319 (SR, HCP): This a quality complaint report (reference number: 312589) as well. A 36-year-old female subject with unknown medical history breast cancer (left sided invasive), cancer surgery, use of chemotherapeutics, radiotherapy, antibody treatment for about one year, hypersensitivity, seasonal allergy (pollen and band aids) was vaccinated with Menveo (batch: 13021, dose not reported) injection NOS. Concomitant medication included tamoxifen. Thirty three days after vaccination, she developed headache (fronto-occipital throbbing with increasing upon standing up), musculoskeletal stiffness (neck), nausea, and vomiting which were treated with ibuprofen, metamizole sodium monohydrate without success. Two days later, she was hospitalized due to **CSF pressure decreased**. On the next day her CSF puncture test revealed that her CSF lactate increased to 2.07 mmol/L (normal value: <1.9), CSF protein increased to 0.621 g/L (normal value: <0.45). On the same day, she also underwent cranial computerized tomogram scan which revealed fluid retention in sinus disorder (right). Intravenous analgesic therapy was not successful. She underwent treatment with theophylline infusion for headache, which later tapered to theophylline oral and caffeine. She also suffered from emotional disorder (strain), which was treated with mirtazapine. Three months and ten days after vaccination, she again experienced neck pain which were treated with tramadol hydrochloride, prochlorperazine, alizapride hydrochloride, and ibuprofen. The outcome of the events headache, neck pain, emotional disorder, and decreased CSF pressure was reported as condition improving; resolved for nausea and vomiting; and not reported for the other events. The reporting physician stated that other unspecified causes were responsible for the reported adverse events and causality was not suspected with vaccination with Menveo. Based on the investigation performed, the QA department stated that, the concerned Menveo vaccine (batch: 13021) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2015CA006455 (SR, non-HCP): This is a quality complaint report (reference number: 348091) as well. An 82-year-old male subject was vaccinated with Menveo (batch: M12106) IM. The vaccine was administered to patient of inappropriate age (off label use). Concomitant medication included darbepoetin-α. Approximately two months after vaccination (two weeks after discontinuing concomitant darbepoetin-α), the subject's **hemoglobin decreased** to 75 (unit not reported) and he developed fatigue and dyspnea. Two months and twelve days after vaccination, he received two units of blood transfusion and seven days later he again received two units when his hemoglobin was reported as 85 (unit not reported). On the same day, he restarted darbepoetin-α 100 mg once every week. The outcome of the event fatigue was condition improving and not reported for dyspnea and hemoglobin decreased. The causality of the events was not reported. Based on the investigation performed, the QA department stated

that, the concerned Menveo vaccine (batch: M12106) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

3.12 Musculoskeletal and connective tissue disorders

During this review period, a total of 83 adverse events from 58 case reports were identified under this body system. Of these, 21 were serious unlisted events. The serious unlisted events identified were arthralgia, arthritis, back pain, extremity contracture, fibromyalgia, joint instability, lower extremity mass, muscular weakness, musculoskeletal discomfort, musculoskeletal stiffness, neck pain, pain in extremity, sensation of heaviness, spinal pain, and synovial cyst.

PHHY2014CA142041 (SR, non-HCP): This is a quality complaint report (reference number: 349312) as well. A 68-year-old female subject with unknown medical history of urinary tract infection (20 years) and arthritis was vaccinated with Menveo (batch: not reported, dose not reported) injection NOS. Approximately seven and a half months later, the subject received two doses of Bexsero (batch: 139201) at an interval of 29 days. Concomitant medications were not reported. Approximately ten months after vaccination with Menveo (second month after vaccination with Bexsero), she experienced nasal congestion for one week (worsens in the morning and at night). Approximately 11 and half months after vaccination with Menveo, she developed urinary tract infection which was treated with cephalexin and ciprofloxacin hydrochloride. Approximately one year and a month after vaccination with Menveo, she experienced pain in extremity leading to gait disturbance (difficulty walking), which was treated with naproxen with some relief. She also experienced **arthritis** (flare-up). On the next day, she experienced dizziness which passed on its own. One week later, her hemoglobin decreased to 66 g/L and she developed a nasopharyngitis, nasal congestion, and productive cough. On the next day, she received two units of transfusion. In the next month, the subject developed respiratory tract congestion. The outcome of the events dizziness and urinary tract infection was resolved; condition improving for pain in extremity, hemoglobin decreased, and respiratory tract congestion; and not reported for the other events. The causality of the events not reported.

PHHY2014DE097350 (SR, HCP): A female subject with unknown medical history was vaccinated with Menveo (batch number and dose not reported) injection NOS. Concomitant medications were not reported. On the fourth day after vaccination, the subject developed lower extremity mass which was diagnosed as **synovial cyst**. The outcome and causality were not reported. Upon follow up, it was confirmed that the subject received meningococcal vaccine of other manufacturer and it was not Menveo. Hence this case would be deactivated.

PHHY2014ES150182 (HA, HCP): A 46-year-old female subject with unknown medical history was vaccinated with Menveo (batch: A90CAA041B, dose not reported) injection NOS. On the same day, the subject also received co-suspect diphtheria and tetanus vaccine (other manufacturer, batch: J73244). Concomitant medications were not reported. Four hours after vaccination, she developed **arthralgia** (lower and upper extremities). Subsequently the subject developed myalgia and asthenia leading to impaired activities of daily living. She was treated with ibuprofen. The outcome of the events was condition unchanged. The HA assessed the events to be suspected to vaccines.

PHHY2014US012634 (SR, HCP): This is a quality complaint report (reference number: 279310) as well. An 11-year-old male subject with medical history of asthma was vaccinated with Menveo (batch: M13012) IM. On the same day, he was also vaccinated with co-suspect influenza virus vaccine polyvalent (other manufacturer, batch: UH899AC). Concomitant medications included montelukast sodium and salbutamol. On the same day after vaccinations, the subject had a fall. He also experienced eye movement disorder, **extremity contracture**, and headache. The outcome of the events was resolved and the causality was not reported. Based on the investigation performed, the QA department stated that, the concerned Menveo vaccine (batch: M13012) was manufactured in accordance with the approved internal procedures and it is in compliance with the cGMP requirements.

PHHY2014US170740 (SR, HCP): This is a quality complaint report (reference number: 345649) as well. A 13-year-old male subject with medical history of acne was vaccinated with Menveo (batch: M14052) IM. On the same day, the subject also received co-suspect hepatitis A vaccine (other manufacturer, batch: K0077921) and tetanus, diphtheria, and pertussis vaccine (other manufacturer, batch: 7KM4D). Concomitant medications were not reported. An unspecified days after vaccinations, the subject developed cough and respiratory tract congestion. Thirty five days after vaccinations, he experienced **muscular weakness**. On the next day, he was hospitalized and diagnosed with CSF white blood cell count increased (lymphocytes 82%), CSF protein increased (123 mg/dL), and nuclear magnetic resonance imaging abnormal. He was treated with intravenous steroids and plasmapheresis with some improvement. The outcome and causality of the events was not reported. Based on the investigation performed, the QA department stated that the concerned Menveo vaccine (batch: M14052) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

3.13 Nervous system disorders

During this review period, a total of 236 adverse events from 155 case reports were identified under this body system. Of these, 44 were serious unlisted events. The serious unlisted events identified were altered state of consciousness, amnesia, burning sensation, clonus, complex regional pain syndrome, convulsion, coordination abnormal, disturbance in attention, dizziness, dysstasia, headache, hypoesthesia, hypotonia, lethargy, loss of consciousness, meningism, migraine, movement disorder, myoclonus, nervous system disorder, paresthesia, polyneuropathy, postictal state, presyncope, radiculopathy, syncope, and tremor.

Table 3-3 15-Day reports from the Nervous system disorders

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
HCP (n=24)							
PHEH20 14US001 741/ SR	11/ M	**Syncope**/ Unresponsive to stimuli/ Vital functions abnormal/ Blood pressure decreased/ Abdominal pain upper	Menveo (batch: M13051) IM	Not reported	Not reported	Not reported	Few minutes after vaccination, the subject developed abdominal pain upper, **syncope**, he was unresponsive to stimuli, his vital functions were abnormal, and his blood pressure decreased. The outcome of the events was reported as resolved and the causality was not reported.
PHEH20 14US011 889/ SR	Unk/ F	**Loss of consciousness**/ Dizziness/ Urinary incontinence/ Vomiting	Menveo (batch: not reported) 0.5 mL IM	Not reported	Fear of injection	Not reported	On the same day after vaccination, the subject developed **loss of consciousness**, dizziness, urinary incontinence, vomiting. The outcome and causality of the events were not reported.
PHEH20 14US012 570/ SR	11/ Unk	**Syncope**	Menveo (batch: M13030) IM	Not reported	Not reported	Not reported	On the same month after vaccination, the subject developed **syncope**. The outcome and the causality of the events were not reported.
PHEH20 14US013 337/ SR	Unk/ Unk	**Syncope**	Menveo (batch: M13030) IM	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **syncope**. The outcome was reported as resolved and the causality was not reported.
PHEH20 14US014 988/ SR	Unk/ Unk	**Loss of consciousness**	Menveo (batch: not reported) injection NOS	Not reported	Not reported	Not reported	On an unknown date after vaccination, the subject developed **loss of consciousness**. The outcome and the causality of the events were not reported.
PHEH20	17/ F	**Convulsion**/	Menveo	diphtheria,	Not reported	Not reported	All the vaccines were received on the same day.

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
14US017016#/ SR		Malaise/ Loss of consciousness/ Postictal state/ Feeling abnormal/ Pallor	(batch: M14031/ X14031) IM	pertussis, and tetanus vaccine (other manufacturer, batch: U4902BA)/ human papilloma vaccine (other manufacturer, batch: K008335)/ ammonia			On the same day after vaccinations, the subject developed **convulsion**, malaise, loss of consciousness, postictal state, pallor, and he was feeling abnormal ("dazed"). The subject was hospitalized due to the events. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHEH2014US018199/ SR	17/ M	**Syncope**	Menveo (batch: A14031/ X14031) 0.5 mL, IM	Not reported	Vaccination history with Menveo which was well tolerated	Not reported	On the same day after vaccination, the subject developed **syncope**. The outcome was reported as resolved and the causality was not reported.
PHFR2014GB005703/ SR	Unk/ Unk	**Syncope**	Menveo (batch: A13094/ X13094) 0.5 mL, IM	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **syncope**. The outcome was reported as resolved and the causality was not reported.
PHFR2014GB005855/ SR	23/ M	**Syncope**/ Dizziness	Menveo (batch: M13103) 0.5 mL, IM	Not reported	Not reported	Not reported	On the same day after vaccination, the subject developed **syncope** and dizziness. The outcome was reported as resolved and the causality was not reported.
PHHY2012DE115126#/ SR	33/ M	**Nervous system disorder**/ Depression/ Performance status decreased/ Musculoskeletal discomfort/	Menveo (batch: M10137) IM	Rabipur® (inactivated rabies virus vaccine) (PCEC)) (batch: 4900 11A) IM	Not reported	typhoid vaccine/ tick-borne encephalitis vaccine/ influenza vaccine/ hepatitis A vaccine in combination with hepatitis B surface	Eleven days after receiving Menveo, the subject administered Rabipur vaccine. An unspecified period after Menveo vaccination the subject developed **nervous system disorder**, depression, musculoskeletal discomfort, headache, nausea, fatigue, asthenia, and his performance status decreased. The outcome of the events was reported as unknown. The

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		Headache/ Nausea/ Fatigue/ Asthenia				antigen/ measles, mumps, and rubella vaccine/ rabies vaccine	causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014AR095688/ SR	11/ M	**Syncope**/ Tonic clonic movements	Menveo (batch: not reported) IM	Not reported	Not reported	diphtheria, pertussis, and tetanus vaccine	On the same day after vaccination, the subject developed **syncope** and tonic clonic movements. The outcome of the events was reported as resolved. The causality of events was suspected to vaccination with Menveo.
PHHY2014AR102213/ SR	11/ F	**Hypotonia**/ Cyanosis/ Vomiting/ Pyrexia	Menveo (batch: not reported) IM	varicella zoster vaccine/ measles, mumps, and rubella vaccine/ hepatitis A vaccine/ pneumococcal vaccine (all other manufacturer and batch not reported)	Not reported	Not reported	All the vaccines were administered on the same day. On the fifth day after the vaccinations, the subject developed **hypotonia**, cyanosis, vomiting, and pyrexia. The subject was hospitalized due to the events. The outcome of the events was reported as resolved and the causality was not reported.
PHHY2014CA149956/ SR	14/ F	**Convulsion**/ Muscle twitching/ Muscle spasms/ Dyskinesia	Menveo (batch: not reported) IM	Not reported	Not reported	ethinylestradiol in combination with levonorgestrel	Ten to 15 minutes after vaccination, the subject developed **convulsion** and dyskinesia. On the same day, she also developed muscle twitching and muscle spasms. The outcome of the events was reported as resolved. The causality of the events was not related to vaccination with Menveo.
PHHY2014CL089349[#]/ SR	Six/ F	**Convulsion**/ Myoclonus/ Cyanosis/ Mastoiditis/ C-reactive protein increased/ Sinusitis	Menveo (batch: M12059) IM	Quinvaxem® (diphtheria, hemophilus influenza type B, hepatitis B, pertussis, and tetanus vaccine) (batch: not	Not reported	polio vaccine/ rotavirus vaccine	Both the vaccines were administered on the same day. Ten hours after vaccinations, the subject developed **convulsion**, myoclonus, and cyanosis. She also developed mastoiditis, sinusitis, and her C-reactive protein increased. The subject was hospitalized due to the events. The outcome of the events was reported as resolved. It was interpreted as an adverse

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
				reported) IM			reaction to vaccines focusing in whole cell pertussis component. Batch review was performed and it did not find any abnormality.
PHHY2014GR111582/ SR	Unk/ Unk	**Syncope**	Menveo (batch: not reported) IM	Not reported	Not reported	Not reported	On an unknown date, after vaccination the subject experienced **syncope**. The outcome and causality were not reported.
PHHY2014GR138777/ SR	13/ M	**Syncope**	Menveo (batch: not reported) IM	Not reported	Stress/ Fear	Not reported	Five minutes after the vaccination, he developed **syncope**. The outcome of the event was resolved. The causality of the event was not suspected to vaccination with Menveo.
PHHY2014IT080681/ HA	15/ M	**Presyncope**/ Headache/ Nausea/ Vomiting	Menveo (batch: M12078) IM	diphtheria, pertussis, and tetanus vaccine (other manufacturer; batch: AC37B1244B)	Not reported	Not reported	Both the vaccines were administered on the same day. Two minutes after vaccinations, the subject developed **presyncope**. He also experienced headache, nausea, and vomiting. The subject was hospitalized due to the events. The outcome of the event was reported as resolved. The causality of the events was suspected to vaccines.
PHHY2014IT147957#/ SR	20/ M	**Polyneuropathy** / Paresthesia/ Myalgia	Menveo (batch: M12067) IM	hepatitis A vaccine (other manufacturer; batch: J05142)	Psychomotor hyperactivity	Not reported	Both the vaccines were administered on the same day. On the 16th day after vaccinations, the subject developed **polyneuropathy** and myalgia. Subsequently, two days later he developed paresthesia. The subject was hospitalized due to the events. The outcome of the events was reported as resolved. The causality of the events was suspected to the vaccines. Batch review was performed and it did not find any abnormality.
PHHY2014US047059#/ SR	16/ F	**Altered state of consciousness**/ Fall	Menveo (batch: M13016)	influenza virus vaccine polyvalent (batch:	Vaccination history of influenza virus	Not reported	All the vaccines were administered on the same day. On the same day after vaccinations, the subject had a fall and developed **altered state of**

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
			injection NOS	UH952AA)/ human papilloma vaccine (batch: J014295)/ hepatitis A vaccine (batch: 494G5); (all other manufacturer)	vaccine		**consciousness**. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US047071[#]/ SR	12/ F	**Presyncope**/ Pallor/ Headache/ Lethargy/ Feeling hot/ Listless/ Somnolence	Menveo (batch: M13015) IM	human papilloma vaccine (batch: J008423)/ influenza vaccine (batch: 5EE73)/ diphtheria, pertussis, and tetanus vaccine (batch: C3989AA); (all other manufacturer)	Not reported	Not reported	All the vaccines were administered on the same day. On the same day after vaccinations, the subject developed **presyncope**, pallor, headache, lethargy, listless, somnolence, and she was feeling hot. The outcome of the event headache was reported as condition unchanged and resolved for the other events. The causality of the events was not reported. Batch review was performed and it did not find any abnormality
PHHY2014US051453[#]/ SR	13/ F	**Complex regional pain syndrome**/ Pain/ Pain in extremity/ Hypoesthesia/ Local swelling/ Tremor/ Fibromyalgia	Menveo (batch: A11072) injection NOS	diphtheria, pertussis, and tetanus vaccine (batch: AC52B099CA)/ human papilloma vaccine (batch: AHPVA169AB)/ varicella virus vaccine, live (batch: H016920); (all other manufacturer)	Tonsillectomy/ Helicobacter infection/ Asthma/ Rhinitis allergic/ Lactose intolerance	Not reported	All the vaccines were administered on the same day. On the second day after vaccinations, the subject developed **complex regional pain syndrome**, pain, pain in extremity, hypoesthesia, peripheral swelling, tremor, and fibromyalgia. The outcome of the events was reported as condition unchanged and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US112572[#]/ SR	18/ M	**Convulsion**/ Loss of consciousness/	Menveo (batch: M13064)	hepatitis A vaccine (batch: 4A53K)/ human	Drug hypersensitivity	Not reported	All the vaccines were administered on the same day. On the same day after vaccinations, the subject developed **convulsion,** loss of

Case ID/ Report type	Age (in years)/ Gender	Reported events (PT)	Vaccine	Co-suspect	Subject History^	Concomitant medications	Comment
		Snoring/ Hyperhidrosis/ Pallor/ Somnolence/ Dizziness	injection NOS	papilloma vaccine (batch: J015378); (all other manufacturer)			consciousness, snoring, hyperhidrosis, pallor, somnolence, and dizziness. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US112682[#]/ SR	13/ F	**Convulsion**/ Loss of consciousness	Menveo (batch: M13030) IM	hepatitis A vaccine (other manufacturer; batch: 9K22D)/ varicella virus vaccine, live (batch: J013728)	diphtheria, tetanus, and pertussis vaccine/ poliovirus inactivated vaccine/ measles, mumps, and rubella vaccine/ Convulsion (Family history)	None	All the vaccines were administered on the same day. On the same day after vaccinations, the subject developed **convulsion** and loss of consciousness. She was hospitalized due to the events. The outcome of the events was reported as resolved and the causality was not reported. Batch review was performed and it did not find any abnormality.
PHHY2014US153219[#]/ SR	16/ F	**Loss of consciousness**/ Dizziness/ Abasia/ Hypoesthesia/ Paresthesia/ Feeling abnormal/ Malaise/ Asthenia/ Pain	Menveo (batch: AT4031) IM	Not reported	Not reported	levothyroxine/ amfetamine aspartate in combination with amfetamine sulfate, dexamfetamine saccharate, and dexamfetamine sulfate	On the same day after vaccination, the subject developed **loss of consciousness,** dizziness, abasia, hypoesthesia, paresthesia, malaise, asthenia, pain, and she was feeling abnormal ("spacey"). The subject was hospitalized due to the events. The outcome of the events was reported as unknown and the causality was not reported. Upon the follow-up from the QA department, it was stated that, the reported Menveo batch: AT4031 was not a valid batch number; hence QA investigation would not be performed.

SR=Spontaneous Report; IM=Intramuscular; HCP=Healthcare Professional; Unk=Unknown; M=Male; F=Female; PT=Preferred Term; HA=Health Authority; NOS=Not Otherwise Specified; *the case was previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and the follow-up was received during the current review period; [#]Quality complaint report; ^Historical condition/ Current condition/ Procedure/ Historical drug; Primary events of the System Organ Class are bold

3.14 Psychiatric disorders

During this review period, a total of 16 adverse events from 13 case reports were identified under this body system. Of these, four were serious unlisted events. The serious unlisted events identified were abnormal dreams, depression, disorientation, and insomnia.

3.15 Reproductive system and breast disorders

During this review period, a total of three adverse events from two case reports were identified under this body system. Of these, two were serious unlisted events. The serious unlisted events identified were ovarian cyst and pelvic pain.

PHHY2013US146758 (SR, HCP): This is a quality complaint report (reference number: 302067) as well. An 11-year-old female subject with unknown medical history was vaccinated with Menveo (batch: M11033, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect human papilloma vaccine (other manufacturer, batch: 1435AA), hepatitis A vaccine (other manufacturer, batch: 1288A), and diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: C4015AA). Concomitant medications were not reported. On an unknown date, she experienced severe epistaxis and headache which continued for few weeks. She also developed a rash and livedo reticularis. One month after vaccinations, she received the second dose of the human papilloma virus vaccine and immediately after vaccination, she developed loss of consciousness. One and half month later, she developed arthralgia, spinal pain, pelvic pain, and pain in extremity. Three days later, she was hospitalized for 11 days with excruciating arthralgia and abasia. Upon admission, her C-reactive protein level was 166 (unit not reported). The subject was treated with morphine, oxycodone, vancomycin, ketorolac tromethamine, and clindamycin. It was reported that 18 months later, she continued experiencing debilitating arthralgia. An MRI scan of pelvic region revealed **ovarian cysts**. The outcome of the events was reported as condition unchanged and the causality was not reported. Based on the batch review performed, the QA department stated that the Menveo (batch: M11033) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

3.16 Respiratory, thoracic and mediastinal disorders

During this review period, a total of 41 adverse events from 30 case reports were identified under this body system. Of these, six were serious unlisted events. The serious unlisted events identified were cough, dyspnea, epistaxis, oropharyngeal pain, and respiratory tract congestion.

PHEH2014US016691 (SR, HCP): This is a quality complaint report (reference number: 330254) as well. A 13-year-old female subject with unknown medical history was vaccinated with one dose of Menveo (batch: M12004/A12004) 0.5 mL IM. Three months and 16 days after vaccination, the subject was administered with another dose of Menveo (batch: A12004) (inappropriate schedule of drug administration) along with co-suspect diphtheria, tetanus, and pertussis vaccine (other manufacturer, batch: T25EG). Concomitant medications were not reported. On the same day after the second dose of vaccination, the subject developed injection site pruritus, diarrhea, abdominal discomfort, somnolence, and **epistaxis**. She was hospitalized for an unspecified duration and she completely recovered from the events. The

causality of the events was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M12004) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2014IT079335 (HA, HCP): A 22-year-old female subject with unknown medical history was vaccinated with meningococcal vaccine (unknown manufacturer, batch number and dose not reported) IM along with co-suspect poliomyelitis vaccine (unknown manufacturer, batch: not reported). Concomitant medications were not reported. On the same date after vaccinations, the subject developed dyspnea and **throat tightness**. She was treated with epinephrine and hydrocortisone sodium succinate with partial benefit. Subsequently, she was admitted to the emergency room and treated with hydrocortisone sodium succinate, chlorphenamine maleate, and omeprazole. Her otorhinolaryngological examination results were normal and discharged from the emergency room. The HA assessed the event as life-threatening. The outcome of the events was reported as resolved. The causality of the events was reported as suspected to be related to administration of vaccines.

3.17 Skin and subcutaneous tissue disorders

During this review period, a total of 202 adverse events from 136 case reports were identified under this body system. Of these, 26 were serious unlisted events. The serious unlisted events identified were blister, ecchymosis, erythema, erythema multiforme, petechie, pruritus, purpura, rash, skin discoloration, skin warm, and swelling face.

PHEH2014US012655 (SR, HCP): This is a quality complaint report (reference number: 315059) as well. A 14-year-old male subject with unknown medical history was vaccinated with Menveo (batch: M13064) 0.5 mL IM. Concomitant medications were not reported. Twelve to 24 hours after vaccination, he developed urticaria and **petechie**. On the next day, the subject was treated with prednisone and antihistamines NOS in the emergency room, but was not hospitalized. The outcome of the events was resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M13064) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2012US099150 (SR, HCP): This is a quality complaint report (reference number: 302323) as well. A 12-year-old male subject's familial history included systemic lupus erythematosus (mother). The subject was vaccinated with Menveo (batch: M11054A, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect diphtheria, pertussis, and tetanus vaccine (other manufacturer, batch: AC52B073CA) and varicella vaccine (other manufacturer, batch: 1798AA). Concomitant medications were not reported. Fifteen days after vaccinations, the child developed pyrexia (101°F), **blister**, and scab. The outcome of the events was resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M11054A) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2013MY141122 (SR, HCP): This case has been previously presented in the Periodic Safety Report for the period of 19 Feb 2013 to 18 Feb 2014 and this is an update. This is a quality complaint report (reference number: not available) as well. A 56-year-old female subject with unknown medical history was vaccinated with Menveo (batch: A12035/ X12035) 0.5 mL IM. Concomitant medications were not reported. On an unspecified date after vaccination, the subject developed **rash generalized** with pain and myalgia. She was prescribed antihistamines NOS and the events resolved. The causality of the events was reported as suspected to the vaccination with Menveo. The QA department stated that this was not a product technical complaint but an adverse event.

Follow-up information received during current review period included update on the QA comment.

PHHY2013US110820 (SR, HCP): This is a quality complaint report (reference number: 257014) as well. A 12-year-old male subject with unknown medical history was vaccinated with Menveo (batch: A12009, dose not reported) IM. On the same day, the subject was also vaccinated with co-suspect varicella vaccine (other manufacturer, batch: J001181), hepatitis A vaccine (other manufacturer, batch: AHAVB520AA), and diphtheria vaccine, pertussis vaccine, and tetanus vaccine (other manufacturer, batch: AC52B092FA). Concomitant medications were not reported. On the second day after vaccination, the subject developed extensive swelling of vaccinated limb, **blister**, and secretion discharge. Subsequently on the next day, he visited to the emergency room and was prescribed sulfamethoxazole with combination of trimethoprim and diphenhydramine hydrochloride. The outcome of the events was resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: A12009) was manufactured in accordance with the approved internal procedures and it was in compliance with the cGMP requirements.

PHHY2014BR146727 (SR, non-HCP): A six-year-old female subject with unknown medical history was vaccinated with Menveo (batch: M14048, dose not reported) IM. Concomitant medications were not reported. On the second day after vaccination, she developed an episode of angioedema and again three days later she developed **angioedema**. The outcome of the event was resolved and the causality was not reported.

PHHY2014GR115504 (HA, HCP): A nine-year-old female subject with unknown medical history was vaccinated with Menveo (batch: not reported) 0.5 mL IM. Concomitant medications were not reported. Eighteen hours after vaccination, the subject developed **purpura** in the face and neck. The outcome of the event was reported as condition improving and the causality was not reported.

PHHY2014US054680 (SR, HCP): This is a quality complaint report (reference number: 298019) as well. A two-year-old male subject with medical history of streptococcal pharyngitis was vaccinated with Menveo (batch: M11081, dose not reported) injection NOS along with hepatitis A vaccine (other manufacturer, batch: J011385). Concomitant medications were not reported. On the next day after vaccinations, the subject developed rash. Subsequently on the next day, his culture was positive for *Streptococcus* and he received treatment with cefdinir. On the fourth day after vaccinations, he experienced episode of diarrhea and went to emergency room. One week after vaccinations, he was diagnosed with

erythema multiforme. The subject was treated with ammonium chloride with combination of diphenhydramine hydrochloride, menthol, and sodium citrate without any improvement. The outcome of the events was reported as resolved and the causality was not reported. Based on the investigation performed, the QA department stated that the Menveo vaccine (batch: M11081) was manufactured in accordance with approved internal procedures and it was in compliance with the cGMP requirements.

3.18 Vascular disorders

During this review period, a total of 23 adverse events from 22 case reports were identified under this body system. Of these, three were serious unlisted events. The serious unlisted events identified were orthostatic hypotension and pallor.

PHHY2014GR020795 (SR, HCP): A 27-year-old female subject with unknown medical history was vaccinated with Menveo (batch number and dose not reported) injection NOS along with co-suspect pneumococcal vaccine (other manufacturer, batch: not reported). Concomitant medications were not reported. On the same day after vaccinations, the subject experienced malaise and pyrexia. On the next day, she developed syncope due to **orthostatic hypotension**. She also developed limb discomfort and movement disorder. The outcome of the event orthostatic hypotension was not reported and resolved for the other events. The causality of the events was not reported.

4 Co-suspect 15-Day-Alerts (reported to other NDAs/BLAs)

A complete list of all cases, where Menveo is listed as a co-suspect medication, is included in Section 9 in a line listing entitled "Cases Sent As FDA 3500As Under Another NDA".

5 Estimate of subject exposure

During this review period, a total of (b) (4) doses of Menveo were sold in the United States.

6 Safety-related labeling changes and other regulatory actions taken since last report

The Menveo package insert was not revised during this review period.

There were no safety-related labeling changes or regulatory actions taken during this review period.

There were no studies initiated or ongoing during the review period due to safety related issues.

7 Conclusion

Based on the data presented in this periodic report and the cumulative experience to date, there is no indication of any changes in the safety profile of Menveo.

8 Prescribing information

The current approved Menveo US Package Insert is provided in Appendix 1.

9 VAERS forms and line listings

VAERS forms and line listings are provided in Appendix 2.

STN: BL 125300; Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

PERIODIC ADVERSE EXPERIENCE REPORT (PAER) SUMMARY

The spontaneous adverse experience reports received during the annual reporting period of February 19, 2015 through February 18, 2016 have been reviewed.

1. NON-ALERT REPORTS

During this reporting period, the following non-alert reports were received:

	Serious Labeled Reports	**Non Serious Labeled Reports**	**Non Serious UnLabeled Reports**
Initial	23 (1)	85	72
Follow-up	0	0	1
Total	23	85	73

() indicates the number of reports submitted in the 15 Day reports section

Reports received from FDA that were processed by Novartis and transferred to the GSK global safety database are included in the non-alert listings since they could not be excluded from GSK's standard PAER output without additional programming efforts. A total of 149 cases fit this criterion, 10 of which inadvertently had in-stream PAERs submitted by GSK.

Please reference **Appendix 1** for an **Index Listing of Non-Alert reports.**

In accordance to the waiver granted by Craig Zinderman on June 3, 2015, a list of individual case safety reports that were previously submitted and their dates of submission are included in **Appendix 2**.

2. ALERT REPORTS

During this reporting period the following 15-Day Alert (3500A) reports were submitted to the Agency:

	15 Day Cases	**15 Day Reports**
Initial	83	83
Follow-up	53	85
Total	104	168

Please reference **Appendix 3, Index Listing of 15-Day Reports by System Organ Class Submitted During Reporting Period**.

There were three (3) cases for Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine] that had unlisted events that were upgraded to serious by GSK upon database transfer from Novartis to GSK. See **Appendix 4** for a listing of these cases.

Follow-up information was received, for cases previously submitted as 15-Day Alert reports, which nullified the case. The GSK case numbers and submission dates are as follows:

GlaxoSmithKline Report Number	**Submission Date**	**Nullification Date**	**Nullification Reason**
GB2016021250	February 16, 2016	March 25, 2016	Duplicate case
GB2016GSK011954	January 29, 2016 February 01, 2016	February 04, 2016	Duplicate case
PHHY2015CA004730	April 20, 2015 May 01, 2015	December 05, 2015	Duplicate case

3. Summary of All Reports

A summary **Tabulation by System Organ Class (SOC**) for all Events Reported is included in **Appendix 5.**

A summary of the ADE reports in which the drug or biological product was listed as one of the suspect drugs, but the report was filed to another NDA/BLA/STN held by GlaxoSmithKline can be referenced in **Appendix 6.**

4. Summary of Actions Taken

During this reporting period, no labeling changes regarding the safety profile of this product have been effected or are pending with the Agency.

A copy of the current prescribing information is provided in **Appendix 7.**

No targeted safety studies have been initiated since the last periodic report.

The following actions have been taken due to safety issues during the reporting period.

- Study V59-34 was completed and found an increased risk of Bell's Palsy. The company has previously included facial paresis in the MenACWYCRM Core Safety Information (CSI) and considers Bell's Palsy to be included as a specific type of facial paresis. The company continues to take a conservative approach with inclusion of Bell's palsy within the CSI, but considers further changes to Menveo labels are not needed

STN: BL 125300; Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

PERIODIC ADVERSE EXPERIENCE REPORT (PAER) SUMMARY

The spontaneous adverse experience reports received during the reporting period of February 19, 2016 through February 18, 2017 have been reviewed.

1. NON-ALERT REPORTS

During this reporting period, the following non-alert reports were received:

	Serious Labeled Reports	**Non Serious Labeled Reports**	**Non Serious UnLabeled Reports**
Initial	0	4	37(1)
Follow-up	0	0	2
Total	0	4	39

() indicates the number of reports submitted in the 15 Day reports section

Please reference Appendix 1 for an **Index Listing of Non-Alert reports.**

In accordance to the waiver granted by Craig Zinderman on May 25, 2016 a list of individual case safety reports that were previously submitted and their dates of submission are included in Appendix 2.

2. ALERT REPORTS

During this reporting period the following 15-Day Alert (VAERS) reports were submitted to the Agency:

	15 Day Cases	**15 Day Reports**
Initial	170	170
Follow-up	42	54
Total	172	224

Please reference Appendix 3, **Index Listing of 15-Day Reports by System Organ Class Submitted During Reporting Period**.

3. Summary of All Reports

A summary **Tabulation by System Organ Class (SOC**) for all Events Reported is included in Appendix 4.

A summary of the ADE reports in which the drug or biological product was listed as one of the suspect drugs, but the report was filed to another NDA/BLA/STN held by GlaxoSmithKline can be referenced in Appendix 5**.**

4. Summary of Actions Taken

During this reporting period, the following labeling changes regarding the safety profile of this product have been effected or are pending with the Agency.

Prior Approval Supplement (PAS) submitted April 05, 2016 and approved October 06, 2016. The prescribing information was updated as follows:

- Addition of information regarding Bell's Palsy added to Adverse Events (6.2 Postmarketing Experience subsection).

A copy of the current prescribing information is provided in Appendix 6.

No targeted safety studies have been initiated since the last periodic report.

The following actions have been taken due to safety issues during the reporting period. There have been no requests from regulatory authorities that place specific safety-related limitations on the development of Menveo.

- An improvement of the vial labeling has been made in order to reduce the number of medication errors (see details in the table below).

Description of the action(s) taken during the reporting period	**Action(s) taken by i.e.: *Sponsor, Regulators, DMC, ECs***	**Status of the action(s) taken**	**Reason for action taken**
Improvement of the readability of the vial labeling	Change in the color scheme of vial labels	Approved by CBER. In the process of implementation on the market	Vaccine administration errors

STN: BL 125300: Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

PERIODIC ADVERSE EXPERIENCE REPORT (PAER) SUMMARY

This report covers the annual reporting period February 19, 2017 through February 18, 2018.

1. NON-ALERT REPORTS

During this reporting period, the following non-alert reports were received:

	Serious Labeled Reports	Non Serious Labeled Reports	Non Serious UnLabeled Reports
Initial	0	0	49
Follow-up	0	0	5
Total	0	0	54

Please reference Appendix 1 for an **Index Listing of Non-Alert reports.**

In accordance to the waiver granted by Craig Zinderman, MD, MPH on July 7, 2017, a list of individual case safety reports that were previously submitted and their dates of submission are included in Appendix 2.

Follow-up information was reported to the Agency in non-alert report(s) that were initially received from the Agency under the VAERS Program. The GlaxoSmithKline case numbers and corresponding FDA reference numbers are as follows:

GlaxoSmithKline Report Number	Reference Type	VAERS Number
PHHY2014US171435	Z_Legacy Reg Authority ID	545822
PHHY2014US171776	Z_Legacy Reg Authority ID	548251
PHHY2015US117231	Z_Legacy Reg Authority ID	558941

2. ALERT REPORTS

During this reporting period, the following 15-Day Alert (VAERS) reports were submitted to the Agency:

	15 Day Cases	15 Day Reports
Initial	180	180
Follow-up	57	80
Total	195	260

STN: BL 125300: Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

Please reference Appendix 3, **Index Listing of 15-Day Reports by System Organ Class Submitted During Reporting Period**.

Follow-up information was reported to the Agency in 15-Day Alert (VAERS) reports that were initially received from the Agency under the VAERS Program. The GSK case numbers and corresponding FDA reference numbers are as follows:

GlaxoSmithKline Report Number	Reference Type	VAERS Number
PHHY2014US170081	Z_Legacy Reg Authority ID	546845
PHHY2015US014110	Z_Legacy Reg Authority ID	551564
PHHY2015US033317	Z_Legacy Reg Authority ID	557812
PHHY2015US034074	Z_Legacy Reg Authority ID	557084
PHHY2015US060340	Z_Legacy Reg Authority ID	568660

3. Summary of All Reports

A summary **Tabulation by System Organ Class (SOC**) for all Events Reported is included in Appendix 4.

A summary of the ADE reports in which the drug or biological product was listed as one of the suspect drugs, but the report was filed to another NDA/BLA/STN held by GlaxoSmithKline can be referenced in Appendix 5**.**

4. Summary of Actions Taken

During this reporting period, no labeling changes regarding the safety profile of this product have been effected or are pending with the Agency.

A copy of the current prescribing information is provided in Appendix 6.

No targeted safety studies have been initiated since the last periodic report.

The following actions have been taken due to safety issues during the reporting period.

No regulatory actions have been taken for safety reasons; however, the following manufacturer actions were taken for safety reasons:

Following the 2017 US FDA inspection carried out at the GSK Rosia site, a retrospective analysis of the filling lines downtime during non-routine interventions (from October 2013 to April 2017), identified technical interventions which have not been simulated during the routine Media Fill process.

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Filling batches were subject to a mechanical intervention, executed during the aseptic filling operations, which was not supported by validation data. Three Menveo batches and two Menjugate batches were impacted by these interventions.

According to the manufacturing site investigation, there was no quality impact on the batches produced.

Besides no safety concern was highlighted during the investigation at global safety level, due to the non-compliance to the cGMP (mechanical intervention executed in aseptic area during filling operations not supported by validation data), the Company anyway decided to conduct, as a precautionary measure, a Class 3 Level 2 recall of the 5 impacted batches.

The review of release parameters (quality control test, environmental and operator monitoring, validation and qualification data) of the impacted batches showed conforming results. In addition, the analysis of technical complaints and medical events received for the associated batches show no signals.

A comprehensive review of data covering the last 3 years from all relevant systems contributing to the sterility assurance at the manufacturing site confirmed that the processes are run in a state of control. GSK therefore confirmed the safety, purity and potency of the batches subject to this recall.

As a consequence of the recall, three batches of Menveo and two batches of Menjugate were withdrawn from the Market:

- Menveo batch number **M16142**, (b) (4) doses distributed in (b) (4)
- Menveo batch number **M16044** (b) (4) doses, distributed in (b) (4) (Note: recall not confirmed by (b) (4)
- Menveo batch number **M16095**, (b) (4) doses, distributed in USA.
- Menjugate batch **155503**, (b) (4) doses distributed to (b) (4)
- Menjugate batch **155702**, (b) (4) doses distributed to (b) (4).

STN: BL 125300; Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

PERIODIC ADVERSE EXPERIENCE REPORT (PAER) SUMMARY

This report covers the annual reporting period February 19, 2018 through February 18, 2019.

1. NON-ALERT REPORTS

During this reporting period, the following non-alert reports were received:

	Serious Labeled Reports	Non Serious Labeled Reports	Non Serious UnLabeled Reports
Initial	0	1	45 (1)
Follow-up	0	0	1
Total	0	1	46

() indicates the number of reports submitted in the 15 Day reports section

Please reference Appendix 1 for an **Index Listing of Non-Alert reports.**

In accordance to the waiver granted by Craig Zinderman, MD, MPH on July 7, 2017 to submit paper VAERS-1 forms in lieu of eVAERS submissions, a list of individual case safety reports that were previously submitted and their dates of submission are included in Appendix 2. The waiver was in effect until July 10, 2018. GSK implemented eVAERS submissions on June 11, 2018.

2. ALERT REPORTS

During this reporting period, the following 15-Day Alert (VAERS and eVAERS) reports were submitted to the Agency:

	15 Day Cases	15 Day Reports
Initial	117	121
Follow-up	25	29
Total	126	150

Please reference Appendix 3, **Index Listing of 15-Day Reports by System Organ Class Submitted During Reporting Period**.

3. Summary of All Reports

A summary **Tabulation by System Organ Class (SOC)** for all Events Reported is included in Appendix 4.

STN: BL 125300; Menveo [Meningococcal (Groups A,C,Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine]

A summary of the ADE reports in which the drug or biological product was listed as one of the suspect drugs, but the report was filed to another NDA/BLA/STN held by GlaxoSmithKline can be referenced in Appendix 5**.** Some cases may be listed twice if there were both VAERS and eVAERS submissions to a different NDA/BLA/STN.

During the period under review, two signals were evaluated:

- One signal was ongoing at the beginning of the PAER reporting period and it was closed during the indicated data lock point (DLP, February 19, 2018 to February 18, 2019); the signal is: Lack of Efficacy of meningococcal vaccines in subjects treated with eculizumab (Soliris)

- One signal was opened and closed during this PAER reporting period; the signal is: Eating disorder symptom (Loss of appetite).

Of these two signals, only *Lack of Efficacy of meningococcal vaccines in subjects treated with eculizumab (Soliris)* was closed as confirmed and led to an update of the Global Data Sheet (GDS). The other signal evaluated in the period was closed as unconfirmed and no GDS update was deemed necessary.

Moreover, a third signal was identified after the DLP of this PAER and it is currently under evaluation; the signal is: Lymphadenopathy.

The three signals are further described below:

- *Lack of Efficacy of meningococcal vaccines in subjects treated with Eculizumab (Soliris)*

  A signal was opened for all marketed meningococcal vaccines upon receipt of the notification from Food and Drug Administration (FDA) on December 20, 2017 that Centre for Biologics Evaluation and Research (CBER) had become aware of cases of meningococcal disease in eculizumab recipients who had been vaccinated with a meningococcal vaccine. Based on CBER review of the available data on these cases, CBER asked GSK, as well as other manufacturers who have a licensed meningococcal vaccine in US, to revise Section 5 (Warnings and Precautions) of the US-package insert (US-PI) to address the risk for meningococcal disease due to the relevant serogroup(s) in vaccinated persons receiving eculizumab. Signal evaluation consisted of individual medical review of cases of vaccination failure occurring in subjects under eculizumab treatment retrieved from the GSK Safety database and review of the published literature. Based on the available data, GSK concluded that individuals treated with eculizumab may remain at risk of invasive meningococcal disease even if they are vaccinated with meningococcal vaccines and an immune response is elicited, because the degree of protection that would be afforded is unknown.

  Due to the seriousness of invasive meningococcal disease, GSK proposed to align with the FDA request and provide a warning statement specifying the risk of invasive meningococcal disease in individuals treated with eculizumab under the section “Warnings and precautions” of the GDS of the four GSK licensed meningococcal vaccines impacted by this signal

evaluation. This signal was closed as confirmed on May 22, 2018. The GDS was updated to include the new warning. The increased risk of invasive meningococcal infection in the eculizumab recipients, linked to the mechanism of action of the drug which induces terminal complement deficiency, does not alter the positive benefit-risk balance for Menveo.

- *Eating disorder symptom (Loss of appetite)*

  During the reporting period, the study V59_77 (A Phase 3b Study to Evaluate Safety and Immunogenicity of a dose of Menveo Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination) was concluded. In this study 'Loss of appetite' was collected as a solicited adverse event in the adolescent/adult age group for the 1st time (in previous studies the evaluation of the safety for Menveo in this age group did not include the collection of this solicited AE). While the other solicited symptoms collected in this study are already listed for this age group, 'Eating disorder' is listed only for infants and children. The results of this study showed a similar proportion of loss of appetite following Menveo administered as a booster or as 1st dose compared to the other listed solicited adverse events collected in this study. Other GSK clinical trials completed outside of the Menveo clinical development program in adolescents and adults were collecting 'Loss of appetite' as a solicited adverse event. To investigate a potential causal association with the vaccine both the clinical trials and the post-marketing Safety databases were queried. From the analysis of all the cases reported in clinical trials where Menveo was administered to adolescents and adults, it was observed that there is no significant difference among the percentages of subjects reporting 'loss of appetite' as solicited adverse event between the Menveo and Placebo groups, i.e., 10% (95% CI: 8.54%-12.36%) and 8% (95% CI: 5.07%-11.59%) respectively. Moreover, it was also noted that a very limited number of subjects reported the occurrence of loss of appetite as an unsolicited adverse event both after receiving Menveo or a Placebo, i.e., <1% (95% CI: 0.05%-0.16%) and <1% (95% CI: 0.00%-0.69%) respectively. From the search of the safety database, a limited number of spontaneous reports, received since Menveo launch, were retrieved. The majority of the cases analysed (clinical data + spontaneous) were not serious and the occurrence of loss appetite was normally reported as resolved. In addition, in most of the cases reported as unsolicited adverse event from clinical trials or as a spontaneous report in the post-marketing experience, at least one concomitant adverse event known to occur with Menveo that might have caused the decreased appetite (i.e., fatigue, nausea or malaise) was reported. Following the analysis of the abovementioned data, it was concluded that there is not enough evidence to suggest a causal association between the occurrence of loss of appetite and the administration of Menveo in adults and adolescents. The signal was closed as unconfirmed on October 26, 2018. Consequently, no GDS update was deemed necessary.

- *Lymphadenopathy*

  A signal was opened on March 2017 upon the monthly routine monitoring of the quantitative signals from (b) (4), i.e., an in-house Vaccines tool designed to detect quantitative signals based on the disproportionality or time to onset (TTO) signal detection methods. Particularly, three cases reporting the Preferred Term (PT) "Lymphadenopathy" were analysed and it was considered that at least one case provided sufficient evidence of a potential causal association with Menveo vaccination. Indeed, the event occurred within a biologically plausible time period and no other causal factor for the event was identified. This case concerned a 28-year-

old female who experienced painful axillary and supraclavicular lymphadenopathy in less than a day after vaccination with Menveo. The serology done to rule out possible aetiological pathogens was negative. On an unknown date, the axillary lymphadenopathy was resolving. The signal evaluation was performed by querying the Clinical Trial and the Post Marketing Safety databases and by literature search. The analysis of available data did not provide sufficient evidence to support a causal association between the occurrence of "Lymphadenopathy" and Menveo vaccination. Thus, the signal was closed and refuted with no impact on the GDS.

On March 11, 2019, GSK received from the European Medicines Agency's Committee for Medicinal Products for Human Use (EMA-CHMP) the final assessment report regarding an Art.46 procedure submitted for the Menveo booster study (V59_77). The Clinical Study Report (CSR) of this study described the occurrence of a single medically attended possibly-related case of "lymphadenopathy" that was considered as possibly related by the investigator. For this reason, EMA requested to add this term in the list of adverse reactions in the Menveo label. Upon this request, it was established to reopen the signal in order to evaluate all the available data and establish if these constitute enough evidence for a causal association between the administration of Menveo and the occurrence of lymphadenopathy. The signal is currently under evaluation and results of the evaluation will be reported in the next version of Menveo PAER.

From the review of data received during the reporting period and presented in this PAER, it has been concluded that the safety profile is adequately reflected in the GDS. No further amendments to the GDS are considered necessary at this time.

The benefit/risk profile of Menveo for active immunization of individuals of children (from 2 months of age), adolescents and adults to prevent invasive meningococcal disease caused by Neisseria meningitides groups A, C, W-135 and Y strains continues to be favorable.

See Section 4 (Summary of Actions Taken) for details on any actions taken.

4. Summary of Actions Taken

During this reporting period, the following labeling changes regarding the safety profile of this product have been effected or are pending with the Agency.

Prior Approval Supplement (PAS) submitted April 6, 2018 and approved October 4, 2018

Effective October 12, 2018, the prescribing information was updated as follows:

- WARNINGS AND PRECAUTIONS was updated to address the increased risk of meningococcal disease in eculizumab recipients even if they have been vaccinated with meningococcal vaccine (Section 5.3 Altered Immunocompetence). Additional editorial revisions were made to previously existing text in Section 5.3 regarding reduced immune response.

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- ADVERSE REACTIONS was updated to include two additional adverse reactions in Section 6.2 Postmarketing Experience ("extensive swelling of the vaccinated limb" and "anaphylaxis").

During the reporting period no safety-related changes to the approved US Product Labelling were pending approval by the CBER. However, on February 20, 2019, two days after the PAER DLP, a submission (STN BLA125300, Sequence 0348) was made to propose changes to the US-PI to comply with the Pregnancy and Lactation Labelling Rule, as well as safety data included for a revaccination study. These labelling changes are currently pending approval by FDA.

A copy of the current prescribing information is provided in Appendix 6.

No targeted safety studies have been initiated since the last periodic report.

The following actions have been taken due to safety issues during the reporting period.

- A precautionary recall of doses of Menveo in study (b) (4) (b) (4) due to potential cracks in vials was internally approved. During the process of preparing doses of study vaccine for shipment to the investigation sites, an issue with the method of transport of study vials between production sites was detected for another study different from (b) (4) which was using the same transportation method. The potential for mechanical stress and ultimately cracks in the vials was identified. Although vaccination of subjects was not started, and no cracks have been reported amongst vials already shipped to study sites, as a precautionary measure, the GSK decided to recall the doses from the potentially impacted Menveo shipment lots from the investigator sites and to replace them with other doses to allow the study to restart.

- Between June 05, 2018 and July 04, 2018, GSK received three product technical complaints from the market in (b) (4) reporting an unusual appearance of the lyophilized Men A component (i.e. it was reported as jellified) of Menveo vaccine lot M16104. None of the doses for which the complaints were submitted was administered. A retain samples check of the Finished Product of Menveo batch M16104 (b) (4) single-dose boxes) was then performed. As a result of this check, three MenA vials with jellified cake were found. After visual analysis of all these three vials, small cracks were identified. Additionally, a secondary manufacturing process review identified an undetected incident occurred during the manual handling of Menveo batch M16104 as the most probable root cause. After this review, it was also concluded that this root cause was limited to the finished Menveo batch M16104 and that no other batches are affected. As a precautionary measure, GSK intends to conduct a Class 2 (Defect may cause mistreatment or harm to the patient, but it is not life-threatening or serious), Level 2 (Retail) recall in (b) (4), upon agreement with (b) (4).

- During the reporting period, the GDS was updated thrice, from Version 006 (dated June 29, 2017) to GDS 009 (dated December 05, 2018). However, the only change in the Core

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Safety Information (CSI) during the reporting interval is in version 007 (dated June 27, 2018). The change to the GDS includes the following:

- Addition of a warning for increased risk to develop Invasive Meningococcal Disease (IMD) in vaccinated individuals receiving treatment that inhibits terminal complement activation such as eculizumab.

PERIODIC ADVERSE EXPERIENCE REPORT (PAER) SUMMARY

This report covers the annual reporting period February 19, 2019 through February 18, 2020.

1. NON-ALERT REPORTS

During this reporting period, the following non-alert reports were received:

	Serious Labeled Reports	Non Serious Labeled Reports	Non Serious UnLabeled Reports
Initial	0	1	36
Follow-up	0	0	0
Total	0	1	36

Please reference **Appendix 1** for an **Index Listing of Non-Alert reports.**

Please reference **Appendix 2** for a **Listing of Non-Alert reports with Submission Dates**

2. ALERT REPORTS

During this reporting period, the following 15-Day Alert (VAERS and eVAERS) reports were submitted to the Agency:

	15 Day Cases	15 Day Reports
Initial	83	83
Follow-up	18	21
Total	87	104

Please reference **Appendix 3**, **Index Listing of 15-Day Reports by System Organ Class Submitted During Reporting Period**.

3. Summary of All Reports

A summary **Tabulation by System Organ Class (SOC**) for all Events Reported is included in **Appendix 4**.

A summary of the ADE reports in which the drug or biological product was listed as one of the suspect drugs, but the report was filed to another NDA/BLA/STN held by GlaxoSmithKline can

be referenced in **Appendix 5.** Some cases may be listed twice if there were both VAERS and eVAERS submissions to a different NDA/BLA/STN.

During the indicated reporting period, as anticipated in the last Menveo PAER (reporting period February 19, 2018 to February 18, 2019), a signal for 'lymphadenopathy' following Menveo administration was evaluated and closed as not refuted warranting an update of the CSI.

In March 2019, following the submission of Menveo V59_77 Clinical Study Report (CSR) to the EMA, according to Article 46 of the EU paediatric regulation (EC) No 1901/2006, in the final Committee of Medicinal Products for Human Use (CHMP) assessment report the Company was requested to add lymphadenopathy in the safety section of the summary of product characteristics (SmPC). The signal for 'Lymphadenopathy' was then opened, evaluated and closed as not refuted.

In this study, a single case of an ipsilateral lymphadenopathy (swollen lymph node under left arm after vaccination in left deltoid) 3 days after receiving Menveo was reported for one subject aged 16 years, among the 701 exposed to Menveo during the study. The event was medically attended and identified by the investigator as possibly related with vaccination.

In the evaluation of the available data, it was observed that, although occurrence is uncommon (<1% from clinical trial database and 0.10 cases per 100,000 doses from spontaneous reports), cases of local lymphadenopathy homolateral to the injection site area have been reported in close temporal relationship (within 24 hours) with administration of Menveo.

Considering these cases, and the biological plausibility of the occurrence of lymphadenopathy following vaccination, it was concluded that the data currently available to GSK suggests an increased risk of lymphadenopathy following vaccination with Menveo. The signal was closed as not refuted leading to the addition of "Local lymphadenopathy" as a new ADR under the MedDRA System Organ Class "Blood and lymphatic system disorders" in the "Post-marketing data" of the "Adverse Reactions" section of the GDS.

From the review of data received during the reporting period and presented in this PAER, it has been concluded that the safety profile is adequately reflected in the GDS. No further amendments to the GDS are considered necessary at this time.

The benefit-risk profile of Menveo for active immunization of individuals from 2 months through 55 years of age against invasive disease caused by N. meningitidis serogroup A, C, W-135 continues to be favorable.

See Section 4 (Summary of Actions Taken) for details on any actions taken.

4. Summary of Actions Taken

During this reporting period, the following labeling changes regarding the safety profile of this product have been effected by the Agency.

Prior Approval Supplement (PAS) was submitted on March 28, 2019 and approved on September 26, 2019

Effective, September 30, 2019, the prescribing information has been updated as follows:

- Addition to Recent Major Changes in the HIGHLIGHTS with corresponding vertical left margin line the full prescribing information to reflect changes in DOSAGE AND ADMINISTRATION.
- Revisions under DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING.
- Annual reportable changes made to correct a superscript in Table 1, and to PATIENT COUNSELING INFORMATION to make the font size consistent throughout the section.

Packaging:

- Changes were made to the design of the outer carton and the container labels for the MenCYW-135 Liquid Conjugate Component and the MenA Lyophilized Conjugate Component, and linear barcodes were added to both container labels.

Prior Approval Supplement (PAS) was submitted on February 20, 2019 and approved on December 20, 2019

Effective January 07, 2020, the prescribing information has been updated as follows:

- Recent major changes added in Highlights for Dosage and Administration, Dosing Schedule (2.3) with corresponding vertical line added to left margin in full prescribing information.
- Safety and immunogenicity data included to support revaccination of adolescents and adults (Highlights, Adverse Reactions, Clinical Studies sections).
- Revisions to comply with the Pregnancy and Lactation Labeling Rule (Use in Specific Populations and Nonclinical Toxicology sections).

Annual reportable changes:

- Removal of outdated recent major change for section 5.3.

Below mentioned is the labeling change pending approval by the FDA:

- At the time of this Menveo PAER there is one safety related Prior Approval Supplement (PAS), submitted on 27 January 2020, that is under pending approval by the FDA concerning the addition of “Local lymphadenopathy” as a new adverse drug reaction (ADR) in the “Post-marketing data” of the “Adverse Reactions” section to reflect the update of the Menveo Global Data Sheet (GDS) version 10.

A copy of the current prescribing information is provided in **Appendix 6**.

No targeted safety studies have been initiated since the last periodic report.

The following actions have been taken due to safety issues during the reporting period.

During the indicated reporting interval, Menveo GDS was updated once from Version 009 (dated December 05, 2018) to GDS Version 010 (dated August 29, 2019). The Core Safety Information (CSI) was updated as follows:

- Addition of "Local lymphadenopathy" as a new Adverse Drug Reaction (ADR) under the MedDRA System Organ Class "Blood and lymphatic system disorders" in the "Post-marketing data" of the "Adverse Reactions" section.

The European Summary of Product Characteristics (EU SmPC) was updated on January 23, 2020 after the input received from the European Medicines Agency (EMA) to add "Lymphadenopathy" as a new ADR under the MedDRA System Organ Class "Blood and lymphatic system disorders" in the "Post-marketing experience" of the "Undesirable effects" section.

During the period under review, no additional actions have been taken due to safety concerns relating to this product in the US or globally.

Protocol Amendment Summary Form

Protocol #: V59P6
Protocol Title: A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with or without Aluminum Phosphate Adjuvant with the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

Proposed Protocol Amendment #: V59P6 Amendment 1
Protocol version being amended: V59P6 – 3 Aug 2004
Other revisions required?

Case Report Form	[ ] Yes	[X] No
Informed Consent Document	[X] Yes	[ ] No

Amendment Rationale:

Chiron seeks additional immunogenicity and safety data on an unadjuvanted formulation of Men ACWY Conjugate vaccine in development.

Update changes in study administrative personnel

Procedural clarifications

Proposed Changes:

PAGE/SECTION *Current page and section number being changed*	**CURRENT** *Language currently in use in protocol*	**PROPOSED CHANGE** *Language proposed*	**JUSTIFICATION** *State specific reason for the change or refer to rationale*
Headers/Footers All Pages	Final Version Number 18, 3 Aug 04	Final Version 4, 01Dec 04	Update document reflect Amendment 1 date
Pg. 1 Title Page; Pg. 3, Study Synopsis Pg. 53, Section 7, Signature page	…Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with the…	…Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine **with or without Aluminum Phosphate Adjuvant** with the…	Update descriptions of study vaccines in the trial (correction repeated where applicable)
Pg. 1 Title Page; Pg. 2, Study Synopsis; Pg. 21 Section 3 Investigators and study administrative structure	Lisa A. Jackson, MD, MPH Center for Health Studies, 1730 Minor Ave., Suite 1600, Seattle, WA 98101	Lisa A. Jackson, MD, MPH **Group Health Cooperative**, Center for Health Studies 1730 Minor Ave., Suite 1600 Seattle, WA 98101	Correct full title of site (correction repeated where applicable)
Pg. 1 Title Page;	Katharina Modelska, MD Phone number: (510) 923-5834	Peter Dull, MD Phone number: (510) 923-3192	Changed Sponsor's Responsible Medical

PAGE/SECTION *Current page and section number being changed*	CURRENT *Language currently in use in protocol*	PROPOSED CHANGE *Language proposed*	JUSTIFICATION *State specific reason for the change or refer to rationale*
Pg. 21 Section 3 Investigators and study administrative structure; Pg. 44 Serious Adverse Events			Officer (correction repeated where applicable)
Pg. 3, Study Synopsis, Study Period; Pg. 25 6.1.2 Planned duration of study	Approximately 14 months overall: 2 months of enrollment and 12 months of individual subject participation	Approximately **17** months overall: **5** months of enrollment and 12 months of individual subject participation	Extended study timeline to reflect additional time due to amendment
Pg. 4, Study Synopsis, Rationale Pg. 22, 5.1 Immunogenicity objectives	The primary objective of this phase 2 study…the Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®),… Chiron Men ACWY Conjugate Vaccine has already been tested in adult and toddler studies…	The primary objective of this phase 2 study…the Chiron Men ACWY Conjugate Vaccine **(with and without aluminum phosphate adjuvant)** with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®),… Chiron Men ACWY Conjugate Vaccine **(with and without aluminum phosphate adjuvant)** has already been tested in adult and toddler studies…	To describe both adjvanted and unadjuvanted Chiron Men ACWY Conjugate Vaccine formulations to be used. Repeated throughout protocol where applicable.
Pg. 4, Study Synopsis, Rationale Pg. 22, 4. Introduction	Overall 120 adults…, of whom approximately 100 subjects received the Men ACWY formulation to be tested in this trial…	Overall 120 adults…, of whom approximately 100 subjects received the **adjuvanted** Men ACWY formulation to be tested in this trial…	To clarify which fomulation of the Chiron Men ACWY Conjugate Vaccine 100 subjects in previous studies received.
Pg. 4, Study Synopsis, Objectives, Immunogenicity Objectives, Primary Objectives/Secondary Objectives 1, 2, and 3; Pg. 22-3, 5.1 Immunogenicity objectives	To compare/evaluate the immunogenicity of a single dose of Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®),…	To compare/evaluate the immunogenicity of a single dose of **either the adjuvanted or unadjuvanted formulation of** Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®),…	To describe both adjvanted and unadjuvanted Chiron Men ACWY Conjugate Vaccine formulations to be used. Repeated throughout protocol where applicable.
Pg. 4, Study Synopsis, Objectives; Pg. 22, 5.1 Immunogenicity	Not present	• Group 1 (Chiron Men ACWY Conjugate Vaccine **WITH** Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)	Group definitions and comparisons added to clarify primary immunogenicity objective

<table>
<tr><td>objectives</td><td></td><td>• Group 3 (Chiron Men ACWY Conjugate Vaccine WITHOUT Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)</td><td></td></tr>
<tr><td>Pg. 4, Study Synopsis, Objectives, Safety Objectives;
Pg. 23, 5.2 Safety Objectives</td><td>To assess the safety and tolerability of a single dose of Chiron Men ACWY Conjugate Vaccine…</td><td>To assess the safety and tolerability of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine…</td><td>To describe both adjvanted and unadjuvanted Chiron Men ACWY Conjugate Vaccine formulations to be used. Repeated where applicable.</td></tr>
<tr><td>Pg. 5, Study Synopsis, Methods, paragraph 1;
Pg. 23, 6.1.1 Overall study design</td><td>This trial is designed as a phase 2,…to evaluate the safety and immune response at one and twelve months following vaccination with either Chiron Men ACWY Conjugate Vaccine or Menomune®…</td><td>This trial is designed as a phase 2,…to evaluate the safety and immune response at one and twelve months following vaccination with one dose of either Chiron Men ACWY Conjugate Vaccine (adjuvanted or unadjuvanted) or Menomune®…</td><td>To describe both adjvanted and unadjuvanted Chiron Men ACWY Conjugate Vaccine formulations to be used. Repeated throughout protocol where applicable.</td></tr>
<tr><td>Pg. 5, Study Synopsis, Methods;
Pg. 23, 6.1.1 Overall study design</td><td>Healthy adolescents will be enrolled and randomized in a 1:1 ratio to one of two vaccination groups and will receive either Chiron Men ACWY Conjugate Vaccine or Menomune®.</td><td>Healthy adolescents will be enrolled and randomized to one of two vaccination groups and will receive either Chiron Men ACWY Conjugate Vaccine or Menomune®. Due to the addition of another study group after enrollment has already begun, the study will be divided into two stages. The first stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine with adjuvant or Menomune® in a 1:1 ratio. The second stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine without adjuvant or Menomune® in a 4:1 ratio. Enrollment in Stage 2 will commence after enrollment inStage 1 has been completed. Other than the randomization ratio, the methodology of the two stages of the study will be identical.</td><td>Statement added to clarify procedure for addition of 3rd study group.</td></tr>
<tr><td>Pg. 5, Study Synopsis, Methods;
Pg. 23, 6.1.1 Overall study design</td><td>Not present</td><td>
<table>
<tr><th>Stage 1 Enrollment</th><th>Description of Treatment Groups</th><th>Number of Subjects Enrolled</th></tr>
<tr><td>Treatment Group 1</td><td>Men ACWY with aluminum phosphate adjuvant</td><td>150</td></tr>
<tr><td>Treatment Group 2</td><td>Menomune</td><td>150</td></tr>
<tr><td colspan="3">Stage 2 Enrollment</td></tr>
<tr><td>Treatment Group 3</td><td>Men ACWY without aluminum phosphate adjuvant</td><td>152</td></tr>
<tr><td>Treatment Group 2</td><td>Menomune</td><td>38</td></tr>
</table>
</td><td>Table added to clarify procedure for addition of 3rd group and estimated group sizes</td></tr>
</table>

<table>
<tr><td></td><td></td><td><table><tr><td>Treatment Group 2</td><td>Menomune</td><td>38</td></tr></table></td><td></td></tr>
<tr><td>Pg. 5, Study Synopsis, Methods;
Pg. 24, 6.1.1 Overall study design</td><td>Subjects in group 1 will receive a single dose of Chiron Men ACWY Conjugate Vaccine administered intramuscularly (IM).</td><td>Subjects in groups 1 and 3 will receive a single dose of Chiron Men ACWY Conjugate Vaccine with or without aluminum phosphate adjuvant, respectively, administered intramuscularly (IM).</td><td>To clarify the addition of the 3rd group and description of both Chiron Men ACWY Conjugate Vaccine formulations</td></tr>
<tr><td>Pg. 5, Study Synopsis, Methods;
Pg. 24, 6.1.1 Overall study design</td><td>The subjects will be instructed to record all AEs whether …..

….only information regarding any SAE, ….</td><td>The subjects will be instructed to record all adverse events (AEs) whether …..

….only information regarding any serious adverse events (SAEs), ….</td><td>The abbreviations for adverse events and serious adverse events were written in full for clarity.</td></tr>
<tr><td>Pg. 6, Study Synopsis, Methods;
Pg. 24, 6.1.1 Overall study design</td><td>The subjects and their parents/legal guardians will be asked to return to the clinic 29 days (Visit 2) after the vaccination.</td><td>The subjects and their parents/legal guardians will be asked to return to the clinic 28 days (Day 29, Visit 2) after the vaccination.</td><td>To correct the timing of return visit, Visit 2.</td></tr>
<tr><td>Pg. 7, Study Synopsis, Number of Subjects Planned
Pg. 26, 6.2 Discussion of overall design</td><td>NUMBER OF SUBJECTS PLANNED:

Approximately 300 subjects will be enrolled to receive either one dose of Chiron MenACWY Conjugate Vaccine or one dose of the licensed control vaccine (Menomune®).</td><td>NUMBER OF SUBJECTS PLANNED:

In the first stage of the study, approximately 300 subjects will be enrolled to receive either one dose of Chiron MenACWY Conjugate Vaccine with adjuvant or one dose of the licensed control vaccine (Menomune®). The second stage will enroll approximately 190 subjects to receive either one dose of Chiron MenACWY Conjugate Vaccine without adjuvant or one dose of the licensed control vaccine (Menomune®). Enrollment in Stage 2 will commence after enrollment in Stage 1 has been completed. The total number enrolled receiving each of the study vaccines will be approximately:

Group 1: Chiron MenACWY Conjugate Vaccine with adjuvant 150

Group 2: Menomune® 188

Group 3: Chiron MenACWY Conjugate Vaccine without adjuvant 152</td><td>Table added to clarify procedure for addition of 3rd group and estimated group sizes</td></tr>
<tr><td>Pg. 9, Study Synopsis, Test Vaccines, Antigen Content, Dosage Regimen, Route of Administration
Pg. 29
6.4.2.1 Vaccines composition</td><td><table><tr><th>Composition</th><th>Quantity per 0.5</th></tr><tr><td>CRM_{197}-MenA</td><td>10 µg MenA, (b) (4)</td></tr><tr><td>CRM_{197}-MenC</td><td>5 µg MenC (b) (4)</td></tr><tr><td>CRM_{197}-MenW</td><td>5 µg MenW, (b) (4)</td></tr><tr><td>CRM_{197}-MenY</td><td>5 µg MenY, (b) (4)</td></tr><tr><td>Aluminum</td><td>0.3 mg Al^{3+}</td></tr></table></td><td><table><tr><th>Composition</th><th>Quantity per 0.5</th></tr><tr><td>CRM_{197}-MenA</td><td>10 µg MenA, (b) (4)</td></tr><tr><td>CRM_{197}-MenC</td><td>5 µg MenC, (b) (4)</td></tr><tr><td>CRM_{197}-MenW</td><td>5 µg MenW, (b) (4)</td></tr><tr><td>CRM_{197}-MenY</td><td>5 µg MenY, (b) (4)</td></tr><tr><td>Aluminum</td><td>0.3 mg Al^{3+}</td></tr></table></td><td>Add additional description for unadjuvanted vaccine formulation</td></tr>
</table>

	phosphate Sodium chloride (b) (4) Sucrose (b) (4) Sodium phosphate buffer (b) (4) Potassium dihydrogen phosphate (b) (4) (b) (4) (b) (4) WFI (b) (4)	phosphate† Sodium chloride (b) (4) Sucrose (b) (4) Sodium phosphate buffer (b) (4) Potassium dihydrogen phosphate (b) (4) (b) (4) (b) (4) WFI (b) (4) **†Formulation without adjuvant identical except aluminum phosphate is not present**	
Pg. 10, Study Synopsis, Reference Vaccines, Antigen Content, Dosage Regimen, Route of Administration Pg. 30 6.4.2.1 Vaccines composition	One 0.5 mL dose of Menomune® is administered subcutaneously.	One 0.5 mL dose of Menomune® **will be** administered subcutaneously **in the left upper arm**.	To clarify the location of the Menomune® injection.
Pg. 11, Study Synopsis, Criteria for Assessing Immunogenicity Objectives	For each serogroup hSBA will be measured and expressed as GMT and percent of subjects with hSBA titer ≥ 1:4.	For each serogroup hSBA will be measured and expressed as GMT and percent of subjects with hSBA **response (i.e., % ≥ 1:4).**	For clarification of percent of hSBA titers.
Pg. 12, Study Synopsis, Statistical Hypothesis; Pg. 49, 6.9.2 Determination of Sample Size	A given Men ACWY serogroup will be assessed to be non-inferior to that serogroup of Menomune® if the lower limit of the one-sided 97.5% confidence interval (CI) around the difference in proportions (Men ACWY *minus* Menomune®) is greater than -10%.	A given Men ACWY serogroup will be assessed to be non-inferior to that serogroup of Menomune® if the lower limit of the **two-sided 95%** confidence interval (CI) around the difference in proportions (Men ACWY *minus* Menomune®) is greater than -10%. **This is equivalent to a one-sided 97.5% CI.**	Clarification of equivalent statements regarding statistical analyses
Pg. 12, Study Synopsis, Statistical Power Considerations Pg. 49-50, 6.9.2 Determination of Sample Size	Power was calculated for various response rates as shown in the table below assuming that 280 subjects (140 per group) provide evaluable samples. The one-sided Type I error rate was set equal to 0.025 and the percent of time the lower limit (LL) of the 95% CI for the difference in proportions (given serogroup for Men ACWY *minus* given serogroup for Menomune®) exceeded -10% was calculated. (b) (4) version (b) (4) was used to perform the calculations	Power was calculated for various response rates as shown in the table below assuming that **175 Menomune** subjects **and 140 Chiron Men ACWY Conjugate Vaccine subjects (either adjuvanted or unadjuvanted)** provide evaluable samples. The one-sided Type I error rate **alpha** was set equal to 0.025 and the percent of time the lower limit (LL) of the 95% CI for the difference in proportions (given serogroup for Men ACWY *minus* given serogroup for Menomune®) exceeded -10% was calculated. (b) (4) version (b) (4) was used to perform the calculations **(rando seed = 1732951, 20000 simulations)**.	Update of power calculation given larger sample size
Pg. 12, Study Synopsis, Statistical Power Considerations; Pg. 50, 6.9.2	Percent of 85% / Percent of 83% / Power that 44%	Percent of 85% / Percent of 83% / Power that **46%**	Update of power calculation given larger sample size

Determination of Sample Size	85% 83% 44% 85% 85% 64% 90% 87% 45% 90% 90% 79% 90% 95% >99% 95% 95% 96%	85% 83% **46%** 85% 85% **67%** 90% 87% **45%** 90% 90% **80%** 90% 95% **>99%** 95% 95% **94%**	
Pg. 12, Study Synopsis, Interim Analysis Pg. 49, 6.9.1.3 Interim analysis planned, 6.9.1.4 Preliminary analysis	No interim analysis of data from this trial is planned. Should it later become necessary, the analyses will be governed by the procedures specified in the Chiron BCDM standard operating procedure entitled "Interim Analysis in a Clinical Trial." A preliminary analysis may be performed to assess the safety and immunogenicity of the study vaccines at one month following vaccination when data collection from all subjects for these time points is complete.	**To facilitate the planning of future trials, before all subjects have completed Visit 2, a group unblinded interim analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization). In addition, a preliminary analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization) after all subjects have completed Visit 2. The results of these analyses will not alter the course of the trial.** The analyses will be governed by the procedures specified in the Chiron BCDM standard operating procedure entitled "Interim Analysis in a Clinical Trial."	Clarify intention that interim and/or preliminary analyses may be performed
Pg. 13, Study Synopsis, Time and Events Table, footnote g, Pg. 24, 6.1.1 Overall Study Design; Pg. 41, 6.5.4.1 Study Procedures	[g]…From Day 8 through Visit 2, record and collect…, any event requiring a physician visit,…From Visit 2 to Visit 3, record and collect…	[g]…From Day 8 **up to** Visit 2, record and collect…, any event requiring a **medical office** visit,…From Visit 2 **through** Visit 3, record and collect…	To clarify adverse event recording and collection requirements.
Pg. 18, Study protocol, Definition of terms	**Month, Day:** Study months are based upon 30-day cycles. The study day refers to the number of days after enrollment, with the day of vaccination being designated Day 1.	**Month, Day:** Study months are based upon 30-day cycles. The study day refers to the number of days after enrollment **plus one day**, with the day of vaccination being designated Day 1.	Clarify study day identification
Pg. 28-9 Section 6.4.1 Vaccines administered	At Visit 1, subjects will be randomly assigned in a 1:1 ratio to one of the following groups: <u>Group 1:</u> Subjects will receive a single dose injection of Chiron Men ACWY Conjugate Vaccine administered IM in the left deltoid. <u>Group 2:</u> Subjects will receive a single dose injection of Menomune® administered SC in the left upper arm.	**Stage 1**: At Visit 1, subjects will be randomly assigned in a 1:1 ratio to one of the following groups: <u>Group 1:</u> Subjects will receive a single dose injection of Chiron Men ACWY Conjugate Vaccine with aluminum phosphate adjuvant administered IM in the left deltoid. <u>Group 2:</u> Subjects will receive a single dose injection of Menomune® administered SC in the left upper arm. **Stage 2**: At Visit 1, subjects will be randomly assigned in a 4:1 ratio to one of the following	Addition of unadjuvanted formulation administration description with stage 2

		groups: <u>Group 3:</u> Subjects will receive a single dose injection of Chiron Men ACWY Conjugate Vaccine without aluminum phosphate adjuvant administered IM in the left deltoid. <u>Group 2:</u> Subjects will receive a single dose injection of Menomune® administered SC in the left upper arm.	
Pg. 32 6.4.2.3 Vaccine administration	• Draw up the diluent into a suitable size syringe (i.e., 2 mL) and inject the contents into the vial containing the lyophilized vaccine;	• Draw **up 0.6 mL** of the **liquid** diluent into a suitable size syringe (i.e., 2 mL) and inject the contents into the vial containing the lyophilized vaccine;	Clarify volume of diluent to be used for reconstitution
Pg. 33 6.4.3 Methods of Assigning Subjects to Vaccination Groups	The study vaccines will be assigned in a 1:1 randomization ratio within each site.	**In the first stage of the study, the Chiron Men ACWY vaccine and Menomune® vaccine** will be assigned in a 1:1 randomization ratio within each site. **In the second stage of the study, Men ACWY and Menomune® will be assigned in a 4:1 ratio.**	Update to include stage 2 subjects being enrolled
Pg. 33 6.4.4 Selection of doses in the study	Preliminary data suggest improved immunogenicity for at least one vaccine antigen component (W) in the presence of adjuvant.	**Although** preliminary data suggest improved immunogenicity for at least one vaccine antigen component (W) in the presence of adjuvant**, this trial will add further data to understand its relative contribution.**	Clarify rationale for additional stage 2 subjects
Pg. 35 6.5.2.1 Immunogenicity variables	The immunogenicity variables are the anti-*N meningitidis* serogroup A, C, W-135, and Y geometric mean titers (GMT) and percentage of subjects with hSBA ≥ 1:4, as measured by hSBA.	**For each serogroup, hSBA will be measured and expressed as GMT and percent of subjects with hSBA response (i.e., % ≥ 1:4). Additional analyses may be performed to further describe the bactericidal response (e.g., % ≥ 1:8). Additional assays to further characterize the immune response to the vaccine components may also be performed.**	Harmonize language between synopsis and full protocol
Pg. 36 6.5.2.2 Safety variables	Local and systemic reactions and other adverse events will be collected.	Local and systemic reactions and other adverse events will be collected. **Safety will be assessed in terms of the number of subjects with reported local and systemic reactions and/or all AEs through Day 7 and/or all SAEs and/or AEs requiring a physician visit and/or resulting in premature withdrawal from the study, per vaccination group through study termination**.	Harmonize language between synopsis and full protocol
Pg. 36 Adverse events	No text	The following are the documentation requirements of adverse events during the different timepoints of the study. From Day 1 through Day 7, record and collect information	Clarify when all adverse events are collected and when only medically significant events are

<table>
<tr><td></td><td></td><td>regarding all adverse events. From Day 8 up to Visit 2 (Day 29), record and collect information regarding any SAE, any event requiring a medical office visit, and any event resulting in a subject's early termination. From Visit 2 through Visit 3, record and collect any SAE, any significant medical event, and any event resulting in a subject's early termination.</td><td>collected</td></tr>
<tr><td>Pg 48 Section 6.9.1.2 Analysis of Safety Criteria</td><td>The power to detect differences between the two groups in rates of any one local or systemic reaction for sample sizes of 150 subjects per group is shown for varying rates in the table below.</td><td>The power to detect differences between the two groups in rates of any one local or systemic reaction for sample sizes of 188 subjects receiving Menomune and 150 subjects receiving Men ACWY (either adjuvanted or unadjuvanted) is shown for varying rates in the table below.</td><td>Update of power calculation given larger sample size</td></tr>
<tr><td>Pg 48 Section 6.9.1.2 Analysis of Safety Criteria</td><td><table><tr><th>Percent of Menomune® subjects with any one local or systemic event (n=188)</th><th>Percent of Men ACWY subjects with any one local or systemic event (n=150)</th><th>Power (2-sided α = 0.05)</th></tr><tr><td>5%</td><td>15%</td><td>82%</td></tr><tr><td>10%</td><td>20%</td><td>68%</td></tr><tr><td>10%</td><td>25%</td><td>93%</td></tr><tr><td>15%</td><td>25%</td><td>58%</td></tr><tr><td>15%</td><td>30%</td><td>87%</td></tr><tr><td>20%</td><td>30%</td><td>51%</td></tr><tr><td>20%</td><td>35%</td><td>83%</td></tr></table></td><td><table><tr><th>Percent of Menomune® subjects with any one local or systemic event (n=188)</th><th>Percent of Men ACWY subjects with any one local or systemic event (n=150)</th><th>Power (2-sided α = 0.05)</th></tr><tr><td>5%</td><td>15%</td><td>86%</td></tr><tr><td>10%</td><td>20%</td><td>73%</td></tr><tr><td>10%</td><td>25%</td><td>95%</td></tr><tr><td>15%</td><td>25%</td><td>63%</td></tr><tr><td>15%</td><td>30%</td><td>91%</td></tr><tr><td>20%</td><td>30%</td><td>56%</td></tr><tr><td>20%</td><td>35%</td><td>87%</td></tr></table></td><td>Update of power calculation given larger sample size</td></tr>
<tr><td>Pgs. 5,6,23,24,25,40,41</td><td>…physical examination…</td><td>…physical examination/assessment…</td><td>Clarify nomenclature to allow non-physician designees (i.e., nurses) to perform physical assessments</td></tr>
<tr><td>All Sections</td><td></td><td><u>Typographical errors and formatting changes have been made throughout the document</u>.</td><td>Administrative changes</td></tr>
</table>

CHIRON | VACCINES

CLINICAL STUDY PROTOCOL V59P6

Amendment No. 1

Final Issued 01 December 2004

A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with or without Aluminum Phosphate Adjuvant with the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

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STUDY SYNOPSIS

TITLE OF STUDY:

A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with or without Aluminum Phosphate Adjuvant with the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

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STUDY PERIOD: **CLINICAL PHASE:**

Approximately 17 months overall:5 months of enrollment and 12 months of individual subject participation — Phase 2

RATIONALE:

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease causes high rates of morbidity and mortality even among patients who receive early antibiotic treatment. Meningococcal meningitis has a case fatality rate of 5% to 10%, and in meningococcal septicemia fatality rate can be as high as 20% to 40%.

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *Neisseria meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, Y, and W_{135} being responsible for the large majority of invasive meningococcal infections worldwide. The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. Currently there is no licensed vaccine in the US for serogroup B, while there is an ACWY polysaccaride vaccine, Menomune® (Aventis Pasteur), licensed for use in children > 2 years of age, and recommended for use in college students (living in dormitories), travelers, and other high risk individuals. As the polysaccharide vaccine induces a largely T-cell independent immune response, the duration of protection is limited (e.g., 2 to 4 years), and hyporesponsiveness to repeated doses has been described.

There is currently no Men ACWY conjugate vaccine licensed for use in the US. Based upon the recent, successful development of conjugate vaccines designed to prevent disease with *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* serogroup C, Chiron is developing a conjugate Men ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM_{197} (a non-toxic mutant of diphtheria toxin).

The primary objective of this phase 2 study is to compare the immunogenicity of a single dose of the Chiron Men ACWY Conjugate Vaccine (with and without aluminum phosphate adjuvant) with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), administered to adolescents 11 to 17 years of age. Chiron Men ACWY Conjugate Vaccine (with and without aluminum phosphate adjuvant) has already been tested in adult and toddler studies and has been shown to be well tolerated and immunogenic. Overall 120 adults and more than 700 toddlers have received at least one dose of the vaccine, of whom approximately 100 subjects received the adjuvanted Men ACWY formulation to be tested in this trial (10μg of serogroup A oligosaccharide, 5μg each of serogroups C, W, and Y oligosaccharide and aluminum

phosphate as an adjuvant). A comprehensive review of Chiron Men ACWY Conjugate Vaccine is contained in the Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

OBJECTIVES:

Immunogenicity Objectives

Primary Objectives

1. To compare the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** after vaccination, when administered to adolescents 11 to 17 years of age.

    - Group 1 (Chiron Men ACWY Conjugate Vaccine **WITH** Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)

    - Group 3 (Chiron Men ACWY Conjugate Vaccine **WITHOUT** Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)

Secondary Objectives

1. To compare the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as SBA geometric mean titer [GMT] antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **1 month** after vaccination, when administered to adolescents 11 to 17 years of age.

2. To evaluate the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y, at **12 months** after vaccination, when administered to adolescents 11 to 17 years of age.

3. To evaluate the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide

vaccine (Menomune®), defined as SBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y, at **12 months** after vaccination, when administered to adolescents 11 to 17 years of age.

Safety Objectives

To assess the safety and tolerability of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine compared to the safety and tolerability of a single dose of Menomune® when administered to adolescents 11 to 17 years of age.

METHODS:

This trial is designed as a phase 2, randomized, single-blind, controlled, multicenter study to evaluate the safety and immune response at one and twelve months following vaccination with one dose of either Chiron Men ACWY Conjugate Vaccine (adjuvanted or unadjuvanted) or Menomune® in healthy adolescents 11 to 17 years of age.

Healthy adolescents will be enrolled and randomized to one of two vaccination groups and will receive either Chiron Men ACWY Conjugate Vaccine or Menomune®. Due to the addition of a third study group after enrollment has already begun, the study will be divided into two stages. The first stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine with adjuvant or Menomune® in a 1:1 ratio. The second stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine without adjuvant or Menomune® in a 4:1 ratio. Enrollment in Stage 2 will commence after enrollment in Stage 1 has been completed. Other than the randomization ratio, the methodology of the two stages of the study will be identical.

Stage 1 Enrollment	**Description of Treatment Groups**	**Number of Subjects Enrolled**
Treatment Group 1	Men ACWY with aluminum phosphate adjuvant	150
Treatment Group 2	Menomune	150
Stage 2 Enrollment		
Treatment Group 3	Men ACWY without aluminum phosphate adjuvant	152
Treatment Group 2	Menomune	38

At the enrollment visit (Visit 1, Day 1), an initial physical examination will be performed and medical history will be obtained from the subjects. In addition, a urine pregnancy test will be conducted for all females of childbearing potential. If in the clinical judgement of the investigator, the subjects are in good health and they meet all inclusion criteria and do not meet any exclusion criteria, they may be enrolled in the study. Prior to adminstration of study vaccine, a blood sample (20 mL) will be obtained for serologic evaluation.

The subjects will then receive the study vaccine by an unblinded study vaccine administrator. The subjects will be blinded to the study vaccine they receive. The study vaccine will be administered in the left upper arm. Subjects in groups 1 and 3 will receive a single dose of Chiron Men ACWY Conjugate Vaccine with or without aluminum phosphate adjuvant, respectively, administered intramuscularly (IM). Subjects enrolled in group 2 will receive a single dose of Menomune® (comparator) administered subcutaneously (SC). Following vaccination, the subjects will be monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, local injection site and systemic reactions.

During this visit, the subjects and their parents/legal guardians will be instructed on how to take their oral temperature daily for 7 days (Day 1 through Day 7) after vaccination at approximately the same time each day. The sponsor will supply the investigators with digital thermometers for distribution to the subjects. In addition, the subjects and their parents/legal guardians will be instructed on how to complete a diary card for 7 days after vaccination. The subjects will be instructed to record **all adverse events** (AEs), whether considered associated or not, associated with the use of the study vaccine for the first 7 days after vaccination. These AEs will include local reactions (i.e., pain, erythema, and induration), systemic reactions (i.e., chills, nausea, malaise, myalgia, arthralgia, and headache), and any other AEs. Their daily oral temperature will also be recorded on the diary card. All concomitant medications (prescription and non-prescription) will be recorded on the diary card for the first 7 days after vaccination. The subject will be instructed that from Day 8 up to Visit 2, only information regarding any serious adverse events (SAEs), any event requiring a physician visit, and any event resulting in a subject's early termination will be required to be recorded on their diary card. Only prescription medications will be collected from Day 8 through Visit 3 or study termination.

At 2 days after vaccination (Day 3), the subjects or the subjects' parents/legal guardians will be contacted by telephone by the investigator or designee to determine the subjects' clinical status and to remind the subjects to record all adverse events (including local and systemic reactions and any other AEs) and concomitant medications on the diary card. The subjects will be asked to report any medical problems that are of concern to them to the investigator or designee at this call.

The subjects and their parents/legal guardians will be asked to return to the clinic 28 days (Day 29, Visit 2) after the vaccination. At this visit, a physical examination will be

performed. A blood sample (20 mL) will be obtained for serologic evaluation. The diary card will be collected at this visit, and the information including AEs and concomitant medications will be reviewed with the subject by the investigator (or designated study nurse). At this visit, the subjects will be provided with a worksheet and instructed to record information regarding any SAEs, any significant medical event (e.g., hospitalizations, Emergency Room visits), any event resulting in a subject's early termination, and any prescription medication taken to treat these events experienced from Visit 2 through Visit 3. Medical office visits for routine medical care, immunization, and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries will not be collected from Visit 2 through study termination. However, if any of these conditions evolves into an SAE, the SAE will be clinically followed, collected, and reported.

At 6 months (Day 180) after vaccination, the investigator or designee will conduct a follow-up phone call to assess the health status of the subject. During this phone call, the subjects will be reminded to record any SAEs and/or significant medical problems and prescription concomitant medications on the worksheet. The subjects will be asked to report any medical problems that are of concern to them to the investigator or designee at this call.

At Day 360 (Visit 3) 12 months following study vaccination, the subjects and their parents/legal guardian will return to the clinic for the study termination visit. At this visit, a physical examination will be performed. A blood sample (20 mL) will be obtained for serologic evaluation. The worksheet will be collected and reviewed again with the subject. All AEs will be monitored until resolution and/or the cause is known. If an AE remains unresolved after Visit 3 or at study termination, a clinical assessment will be made by the investigator and the Chiron Medical Monitor to determine whether continued follow up of the AE is warranted.

NUMBER OF SUBJECTS PLANNED:

In the first stage of the study, approximately 300 subjects will be enrolled to receive either one dose of Chiron MenACWY Conjugate Vaccine with adjuvant or one dose of the licensed control vaccine (Menomune®). The second stage will enroll approximately 190 subjects to receive either one dose of Chiron MenACWY Conjugate Vaccine without adjuvant or one dose of the licensed control vaccine (Menomune®). Enrollment in Stage 2 will commence after enrollment in Stage 1 has been completed. The total number enrolled receiving each of the study vaccines will be approximately:

Group 1: Chiron MenACWY Conjugate Vaccine with adjuvant 150

Group 2: Menomune® 188

Group 3: Chiron MenACWY Conjugate Vaccine without adjuvant 152

SUBJECT CHARACTERISTICS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Healthy adolescents will be recruited from the local communities.

Inclusion Criteria

Adolescents (male and female) eligible to be enrolled in the study are those:

1. who are between 11 and 17 years of age inclusive and are available for all visits and telephone calls scheduled for the study;

2. who have given written assent and/or for whom the parent or legal guardian has provided written informed consent after the nature of the study has been explained;

3. who are in good health as determined by:

    - medical history
    - physical examination
    - clinical judgment of the investigator

Exclusion Criteria

Adolescents not eligible to be enrolled in the study are those:

1. who or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;

2. who had a previous suspected disease caused by *N meningitidis*;

3. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* serogroup A, C, W, and/or Y infection within 60 days prior to enrollment;

4. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational);

5. who have received any investigational agents or vaccines 90 days prior to enrollment;

6. who have received any licensed vaccines within the 30 days prior to enrollment or for whom receipt of a licensed vaccine is anticipated within the 30 days after vaccination. *(Exception: Influenza vaccine may be administered 15 days prior to study vaccination and 15 days after study vaccination)*;

7. who plan to receive the recommended vaccines such as Td/Hep B series, MMR, Varicella, or Hep A series between Visit 1 and Visit 2. (Recommended vaccines for this age group may be administered after the blood draw at Visit 2);

8. with any serious acute illness;

9. who are pregnant or nursing (breastfeeding) mothers or females of childbearing age who have not used or do not plan to use acceptable birth control measures, as determined by the investigator for the 12-month duration of the study. Abstinence is considered an acceptable form of contraception. (Females will have a urine pregnancy test sensitive to 20 IU β-hCG at entry);

10. with any serious chronic or progressive disease (e.g., any history of neoplasm, insulin-dependent diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids are not eligible for enrollment);

11. with epilepsy or any progressive neurological disease;

12. with a history of any anaphylactic shock, pulmonary reactivity, urticaria, or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;

13. with a known or suspected disease of the immune system, or those receiving immunosuppressive therapy, including use of any systemic corticosteroids, or those who have received blood, blood products, or a parenteral immunoglobulin preparation within 60 days prior to study enrollment;

14. who have taken systemic antibiotics (either oral or parenteral) within the previous 14 days (Exception: subjects who have received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.] may be enrolled 7 days after the last dose);

15. known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

16. with Down's syndrome or other known cytogenic disorders;

17. with an oral temperature of 38.0°C (100.4°F) or more within 3 days prior to study entry;

18. with any condition that, in the opinion of the investigators, might interfere with the evaluation of the study objectives.

Reason for delaying subsequent blood draws:
Development of any condition specified in the initial exclusion criterion 14 cited above.

TEST VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

The investigational Chiron Men ACWY Conjugate Vaccine is obtained by extemporaneous mixing of the lyophilized Men A component to be re-suspended with the Men CWY liquid component. The vaccine should be prepared just prior to administration to the study subject.

After reconstitution, Chiron Men ACWY Conjugate Vaccine will have the following composition per 0.5 mL of injectable suspension:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Aluminum phosphate†	0.3 mg Al^{3+}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
(b) (4)	(b) (4)
WFI	(b) (4)

†Formulation without adjuvant identical except aluminum phosphate is not present

One 0.5 mL dose of the Chiron Men ACWY vaccine will be injected IM in the left deltoid.

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Menomune® (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single dose (one vial of vaccine and one vial of diluent). The vaccine consists of four meningococcal capsular polysaccharide serogroups (A, C, Y and W-135). After reconstitution with the liquid diluent, Menomune® will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
Isolated product from each of groups A, C, Y, and W-135	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: WFI	Qs to 0.5 mL

One 0.5 mL dose of Menomune® will be administered subcutaneously in the left upper arm.

DURATION OF TREATMENT:

Single-dose injection

CONCOMITANT VACCINES:

No concomitant vaccines will be administered from enrollment to Visit 2. Normal routine or catch-up immunizations appropriate for this age group (e.g., vaccines to prevent hepatitis B, tetanus, measles, mumps, rubella and varicella) or other recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria (i.e., vaccines to prevent hepatitis A, influenza or pneumococcal infection) may be administered after the blood draw at Visit 2. *(Exception: Influenza vaccine may be administered 15 days prior to study immunization and 15 days after study immunization).*

MEASURES OF IMMUNOGENICITY:

The ability of Men ACWY Conjugate Vaccine to elicit functional serum bactericidal activity (SBA) against each serogroup in the presence of human complement (hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed.

MEASURES OF SAFETY:

The measures of safety to be used in this study consist of local and systemic reactions and other adverse events.

The assessment of local reactions will include: pain, erythema, and induration. The assessment of systemic reactions will include: chills, nausea, malaise, myalgia, arthralgia, and headache.

SEROLOGY:

The SBA will be performed at:

Chiron Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg, Germany
Phone: 011 49 6421 39 3439/3712

CRITERIA FOR ASSESSING IMMUNOGENICITY OBJECTIVES:

For each serogroup, hSBA will be measured and expressed as GMT and percent of subjects with hSBA response (i.e., % ≥ 1:4). Additional analyses may be performed to further describe the bactericidal response (e.g., % ≥ 1:8).

CRITERIA FOR ASSESSING SAFETY OBJECTIVES:

Safety will be assessed in terms of the number of subjects with reported local and systemic reactions and/or all AEs through Day 7 and/or all SAEs and/or AEs requiring a physician visit and/or resulting in premature withdrawal from the study, per vaccination group through study termination.

STATISTICAL HYPOTHESIS:

The null hypothesis associated with the primary immunogenicity objective is that the proportion of subjects who are responders (i.e., hSBA titer ≥ 1:4) to Men ACWY (either adjuvanted or unadjuvanted) is inferior to the proportion of subjects who are responders on Menomune® for the same serogroup. A given Men ACWY serogroup will be assessed to be non-inferior to that serogroup of Menomune® if the lower limit of the two-sided 95% confidence interval (CI) around the difference in proportions (Men ACWY *minus* Menomune®) is greater than -10%. This is equivalent to a one-sided 97.5% CI.

STATISTICAL POWER CONSIDERATIONS:

Power was calculated for various response rates as shown in the table below assuming that 175 Menomune subjects and 140 Chiron Men ACWY Conjugate Vaccine subjects (either adjuvanted or unadjuvanted) provide evaluable samples. The one-sided Type I error rate alpha was set equal to 0.025 and the percent of time the lower limit (LL) of the 95% CI for the difference in proportions (given serogroup for Men ACWY *minus* given serogroup for Menomune®) exceeded -10% was calculated. (b) (4) version (b) (4) was used to perform the calculations (random seed = 1732951, 20000 simulations).

Percent of responders in one serogroup of Menomune: P1 (n=175)	Percent of responders in one serogroup of Men ACWY: P2 (n=140)	Power that the LL exceeds -10% (1-sided $\alpha = 0.025$)
85%	83%	46%
85%	85%	67%
90%	87%	45%
90%	90%	80%
90%	95%	>99%
95%	95%	94%

INTERIM/PRELIMINARY ANALYSIS:

To facilitate the planning of future trials, before all subjects have completed Visit 2, a group unblinded interim analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization). In addition, a preliminary analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization) after all subjects have completed Visit 2. The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Chiron BCDM standard operating procedure entitled “Interim Analysis in a Clinical Trial.”

TIME AND EVENTS TABLE:

Visit Number **Study Day**	1 1	☎ 3	2 29	☎ 180	3 360
(Range)	(1)	(2 to 4 days after Visit 1)	(28 to 35 days after Visit 1)	(164 to 194 days after Visit 1)	(344 to 374 days after Visit 1)
Procedures					
Obtain Informed Consent	x				
Medical History	x				
Physical Examination[a]	x		x		x
Obtain Blood Sample	x		x		x
Administer Study Vaccine[b]	x				
Injection-site Examination[c]	x		x		x
Assess Local and Systemic Reactions[d]	x		x		
Concomitant Medications	x[e]	x[e]	x[f]		x[f]
Adverse Events [g]	x	x	x	x	x
Study Termination					x

Note: Day 1 is defined as day of study vaccination.

[a] The physical examinations at Visits 1, 2 and 3 (Study Days 1, 29 and 360) should be performed by a study physician or a designated study nurse.

[b] The study vaccine, Chiron Men ACWY Conjugate Vaccine will be administered IM into the subjects left deltoid or a licensed meningococcal vaccine, Menomune®, will be administered SC into the subject's left upper arm. All subjects will be observed in the clinic for 30 minutes after vaccination.

[c] Inspect the injection site at all study visits.

[d] Local and systemic reactions following vaccination will be noted by subjects in the diary cards daily for 7 days after vaccination (Study Days 1 through 7). The diary cards will be reviewed during the Day 3 follow-up phone interview and collected at Visit 2.

[e] Collect data on concomitant medications (prescription and non prescription) through the first 7 days.

[f] Collect data on concomitant medications (prescriptions only) from Day 8 through Visit 3.

[g] From Day 1 through Day 7, record and collect information regarding **all AEs**. From Day 8 up to Visit 2, record and collect information regarding any SAE, any event requiring a medical office visit, and any event resulting in a subject's early termination. From Visit 2 through Visit 3, record and collect any SAE, any significant medical event, and any event resulting in a subject's early termination.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse Event
AP	(Statistical) Analysis Plan
β-hCG	beta human chorionic gonadotropin
BCDM	Biostatistics and Clinical Data Management
CFR	Code of Federal Regulations
CI	Confidence Interval
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HIPAA	Health Insurance Portability and Accountability Act
hSBA	Serum Bactericidal Activity (Assays) using an exogenous human complement source
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention to Treat
LL	Lower Limit
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat
PP	Per Protocol
SAE	Serious Adverse Event
SBA	Serum Bactericidal Activity
SC	Subcutaneous
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO	World Health Organization

Definitions of terms

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

Local and systemic reactions: Selected local and systemic AEs are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within a specified period of time after vaccination are herein termed "local and systemic reactions."

Month, Day: Study months are based upon 30-day cycles. The study day refers to the number of days after enrollment plus one day, with the day of vaccination being designated Day 1.

Serious Adverse Event: A serious adverse event (SAE) is any experience or reaction that suggests a significant hazard, contraindication, side effect, or precaution. These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital anomaly, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate medical judgment, may jeopardize the subject. Vaccine failure should also be considered as a serious adverse event.

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. Chiron Vaccines is part of Chiron Corporation.

End of Trial: The End of Trial corresponds to the last visit of the last subject undergoing the trial (Last Subject Last Visit, LSLV).

2. ETHICS

2.1 Approval of Study Protocol

Chiron or the Investigator will provide the ethics committee (EC) or institutional review board (IRB) with all appropriate material, including the informed consent document, according to the local regulation. The EC or IRB should also be asked for a written statement regarding the composition of the committee. The trial will not be initiated until appropriate EC or IRB approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. Prior to enrollment, the Sponsor and the Investigator must exchange written confirmation that their ethical and legal responsibilities have been observed. The EC or IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. Appropriate reports on the progress of the study will be made to the EC or IRB and the Sponsor by the Investigator in accordance with applicable governmental regulations and in agreement with policy established by the Sponsor.

2.2 Ethical conduct and Good Clinical Practice

The procedures established in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of Good Clinical Practice (GCP) established by the International Conference on Harmonization (ICH), the Declaration of Helsinki, and the Standard Operating Procedures of the Sponsor. A copy of the GCP and ICH guidelines will be included in the Investigator's Study File.

2.3 Informed Consent of Subject and Confidentiality

2.3.1 Informed Consent and Assent of Subject

A properly executed, written, informed consent, in compliance with the Declaration of Helsinki, ICH-GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA) and applicable regulations, will be obtained from each subject prior to entering the subject into the trial. The informed consent form (ICF) and the HIPAA authorization must be signed and dated by the subject and/or parent/legal guardian, and must be countersigned by the person who conducted the informed consent discussion (according to local regulations). If the subject is unable to read, an impartial witness is to be present during the meeting in which the significance of the informed consent will be orally explained to both the subject and his/her parent/legal guardian. The witness, by signing the ICF, will attest that the information in the ICF and any other written information was accurately explained, and apparently understood by the subject and the parent/legal guardian, and that the informed consent was given freely. Additionally, written information about the study will also be provided to all subjects

enrolled. All subjects and their parent/legal guardian will provide assent (or consent where applicable) in addition to providing informed consent.

A copy of the informed consent document will be submitted by the Investigator to the IRB for review and approval prior to the start of the study. The Investigator will provide a copy of the signed informed consent to each of the subjects, and will maintain the original in the subject's record file. The subject is to be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical study. The communication of this information is to be documented. Any revision to the written ICF, or accompanying literature, should receive the IRB's approval.

2.3.2 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject numbers and subject initials will be recorded in the Case Report Form (CRF), and if a subject's name appears on any other document (e.g. pathologist report), it will be obliterated before the copy of the document is supplied to the Sponsor. Study findings stored on a computer will be subject to local data protection laws. The subjects will be informed that representatives of the Sponsor, EC or IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

The Investigator or designee will maintain a personal list of subject numbers and subject names (Subject Identification Code List) to enable records to be found at a later date.

2.4 Liability and Insurance

The involved parties will be insured, in accordance with applicable laws and regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. The Sponsor will provide adequate insurance for the Investigator according to regulatory requirement(s). If required by local law, study subjects enrolled into this clinical trial will also be insured against any injury resulting from the clinical study.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The trial will be administered and monitored by employees or representatives of the sponsor. Clinical Research Associates (CRAs) will monitor each site on a periodic basis and perform verification of source documentation for each subject. The Medical Monitor is responsible for oversight of the general conduct of the trial including subject safety and data integrity.

Prior to trial initiation, the investigator at each site must provide to Chiron a fully executed and signed FDA Form 1572, *Curriculum Vitae*, and a Financial Disclosure

Form. Financial Disclosure Forms must also be completed for all sub-investigators listed on the Form 1572 who will be directly involved in the treatment or evaluation of research subjects in this trial.

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4. INTRODUCTION

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease causes high rates of morbidity and mortality even among patients who receive early antibiotic treatment. Meningococcal meningitis has a case fatality rate of 5% to 10%, and in meningococcal septicemia fatality rate can be as high as 20% to 40%.(1),(2),(3),(4),(5),(6)

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *Neisseria meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, Y, and W_{135} being responsible for the large majority of invasive meningococcal infections worldwide.(7),(4),(5),(8),(9),(10),(11) The best option for the control of meningococcal disease is the use of effective vaccines that

would include all five of the most common serogroups responsible for invasive disease.(12),(13) Currently there is no licensed vaccine in the U.S. for serogroup B, while there is an ACWY polysaccharide vaccine, Menomune® (Aventis Pasteur), licensed for use in children > 2 years of age, and is recommended for use in college students (living in dormitories), travelers, and other high risk individuals. As the polysaccharide vaccine induces a largely T-cell independent immune response, the duration of protection is limited (e.g., 2 to 4 years), and hyporesponsivness to repeated doses has been described.(14),(15),(16),(17)

There is currently no Men ACWY Conjugate Vaccine licensed for use in the US. Based upon the recent, successful development of conjugate vaccines designed to prevent disease with *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* serogroup C,(18),(19) Chiron is developing a conjugate Men ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, Y, and W conjugated to a protein carrier CRM_{197} (a nontoxic mutant of diphtheria toxin).

The primary objective of this phase 2 study is to compare the immunogenicity of the Chiron Men ACWY Conjugate Vaccine (with and without aluminum phosphate adjuvant) with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®) administered to adolescents 11 to 17 years of age. Chiron Men ACWY Conjugate Vaccine (with and without aluminum phosphate adjuvant) has previously been tested in four studies of adults and toddlers and has been shown to be well tolerated and immunogenic. Overall 120 adults and more than 700 toddlers have received at least one dose of the investigational vaccine, of whom approximately 100 toddlers received the adjuvanted Men ACWY formulation to be tested in this trial (10μg of serogroup A oligosaccharide and 5μg each of serogroups C, W, and Y oligosaccharide with aluminum phosphate adjuvant), and 100 toddlers received a higher dose of the adjuvanted formulation (10μg of oligosaccharide for each antigen).

5. STUDY OBJECTIVES

5.1 Immunogenicity Objectives

Primary Objectives

1. To compare the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y at **1 month** after vaccination, when administered to adolescents 11 to 17 years of age.

- Group 1 (Chiron Men ACWY Conjugate Vaccine **WITH** Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)

- Group 3 (Chiron Men ACWY Conjugate Vaccine **WITHOUT** Aluminum Phosphate Adjuvant) vs. Group 2 (Menomune®)

Secondary Objectives

1. To compare the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine with the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), defined as SBA geometric mean titer [GMT] antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y at **1 month** after vaccination, when administered to adolescents 11 to 17 years of age.

2. To evaluate the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®), (defined as percentage of subjects with serum bactericidal activity [i.e., hSBA ≥ 1:4] directed against *N meningitidis* serogroups A, C, W-135, and Y) at **12 months** after vaccination, when administered to adolescents 11 to 17 years of age.

3. To evaluate the immunogenicity of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine and the immunogenicity of a single dose of licensed meningococcal ACWY polysaccharide vaccine (Menomune®) (defined as SBA GMT antibody response directed against *N meningitidis* serogroups A, C, W-135, and Y) at **12 months** after vaccination, when administered to adolescents 11 to 17 years of age.

5.2 Safety Objectives

To assess the safety and tolerability of a single dose of either the adjuvanted or unadjuvanted formulation of Chiron Men ACWY Conjugate Vaccine compared to the safety and tolerability of a single dose of Menomune® when administered to adolescents 11 to 17 years of age.

6. OVERALL STUDY DESIGN

6.1 Overall Study Design and Plan – Description

6.1.1 Overall Study Design

This trial is designed as a phase 2, randomized, single-blind, controlled, multicenter study to evaluate the safety and immune response at one and twelve months following vaccination with one dose of either Chiron Men ACWY Conjugate Vaccine (adjuvanted or unadjuvanted) in healthy adolescents 11 to 17 years of age.

Healthy adolescents will be enrolled and randomized to one of two vaccination groups and will receive either Chiron Men ACWY Conjugate Vaccine or Menomune®. Due to the addition of another study group after enrollment has already begun, the study will be divided into two stages. The first stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine with adjuvant or Menomune® in a 1:1 ratio. The second stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine without adjuvant or Menomune® in a 4:1 ratio. Enrollment in Stage 2 will commence after enrollment in Stage 1 has been completed. Other than the randomization ratio, the methodology of the two stages of the study will be identical.

Stage 1 Enrollment	**Description of Treatment Groups**	**Number of Subjects Enrolled**
Treatment Group 1	Men ACWY with aluminum phosphate adjuvant	150
Treatment Group 2	Menomune	150
Stage 2 Enrollment		
Treatment Group 3	Men ACWY without aluminum phosphate adjuvant	152
Treatment Group 2	Menomune	38

At the enrollment visit (Visit 1, Day 1), an initial physical examination/assessment will be performed and medical history will be obtained from the subjects. In addition, a urine pregnancy test will be conducted for all females of childbearing potential. If in the clinical judgement of the investigator, the subjects are in good health and they meet all inclusion criteria and do not meet any exclusion criteria, they may be enrolled in the

study. Prior to adminstration of study vaccine, a blood sample (20 mL) will be obtained for serologic evaluation.

The subjects will then receive the study vaccine by an unblinded study vaccine administrator. The subjects will be blinded to the study vaccine they receive. The study vaccine will be administered in the left upper arm. Subjects in groups 1 and 3 will receive a single dose of Chiron Men ACWY Conjugate Vaccine with or without aluminum phosphate adjuvant, respectively, administered intramuscularly (IM). Subjects enrolled in group 2 will receive a single dose of Menomune® (comparator) administered subcutaneously (SC). Following vaccination, the subjects will be monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, local injection site and systemic reactions.

During this visit, the subjects and their parents/legal guardians will be instructed on how to take their oral temperature daily for 7 days (Day 1 through Day 7) after vaccination at approximately the same time each day. The sponsor will supply the investigators with digital thermometers for distribution to the subjects. In addition, the subjects and their parents/legal guardians will be instructed on how to complete a diary card for 7 days after vaccination. The subjects will be instructed to record **all adverse events (**AEs), whether considered associated or not, associated with the use of the study vaccine for the first 7 days after vaccination. These AEs will include local reactions (i.e., pain, erythema, and induration), systemic reactions (i.e., chills, nausea, malaise, myalgia, arthralgia, and headache), and any other AEs. Their daily oral temperature will also be recorded on the diary card. All concomitant medications (prescription and non-prescription) will be recorded on the diary card for the first 7 days after vaccination. The subject will be instructed that from Day 8 up to Visit 2, only information regarding any serious adverse events (SAEs), any event requiring a medical office visit, and any event resulting in a subject's early termination will be required to be recorded on their diary card. Only prescription medications will be collected from Day 8 through Visit 3 or study termination.

At 2 days after vaccination (Day 3), the subjects or the subjects' parents/legal guardians will be contacted by telephone by the investigator or designee to determine the subjects' clinical status and to remind the subjects to record all adverse events (including local and systemic reactions and any other AEs) and concomitant medications on the diary card. The subjects will be asked to report any medical problems that are of concern to them to the investigator or designee at this call.

The subjects and their parents/legal guardians will be asked to return to the clinic 28 days (Day 29, Visit 2) after the vaccination. At this visit, a physical examination/assessment will be performed. A blood sample (20 mL) will be obtained for serologic evaluation. The diary card will be collected at this visit, and the information including AEs and concomitant medications will be reviewed with the subject by the investigator (or designated study nurse). At this visit, the subjects will be provided with a worksheet and

instructed to record information regarding any SAEs, any significant medical event (e.g., hospitalizations, Emergency Room visits), any event resulting in a subject's early termination, and any prescription medication taken to treat these events experienced from Visit 2 through Visit 3. Medical office visits for routine medical care, immunization, and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis, and traumatic injuries will not be collected from Visit 2 through study termination. However, if any of these conditions evolves into an SAE, the SAE will be clinically followed, collected, and reported.

At 6 months (Day 180) after vaccination, the investigator or designee will conduct a follow-up phone call to assess the health status of the subject. During this phone call, the subjects will be reminded to record any SAEs and/or significant medical problems and prescription concomitant medications on the worksheet. The subjects will be asked to report any medical problems that are of concern to them to the investigator or designee at this call.

At Day 360 (Visit 3) 12 months following study vaccination, the subjects and their parents/legal guardian will return to the clinic for the study termination visit. At this visit, a physical examination/assessment will be performed. A blood sample (20 mL) will be obtained for serologic evaluation. The worksheet will be collected and reviewed again with the subject. All AEs will be monitored until resolution and/or the cause is known. If an AE remains unresolved after Visit 3 or at study termination, a clinical assessment will be made by the investigator and the Chiron Medical Monitor to determine whether continued follow up of the AE is warranted.

6.1.2 Planned Duration of Study

Expected subject enrollment interval: 5 months

Duration of individual subject's participation: 12 months

Total duration of study: 17 months

End of Trial: corresponds to the last visit of the last subject undergoing the trial (LSLV).

6.1.3 Premature Discontinuation of the Study

The Sponsor or the Investigator (following consultation with the Sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the Investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study medication/vaccines etc.) will be returned to the Sponsor.

6.2 Discussion of Overall Study Design

This is a phase 2, randomized, single-blind, controlled, multicenter study to evaluate the safety and immune response at one and twelve months following vaccination with a single dose of either Chiron Men ACWY Conjugate Vaccine (adjuvanted or unadjuvanted) or Menomune® in healthy adolescents 11 to 17 years of age.

Healthy adolescents will be enrolled and randomized to receive either one dose of the investigational Chiron Men ACWY Conjugate Vaccine administered intramuscularly (IM) or one dose of the currently licensed meningococcal ACWY polysaccharide vaccine, Menomune®, administered subcutaneously (SC). Due to the addition of a third study group after enrollment has already begun, the study will be divided into two stages. The first stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine with adjuvant or Menomune® in a 1:1 ratio. The second stage will randomize subjects to receive either Chiron Men ACWY Conjugate Vaccine without adjuvant or Menomune® in a 4:1 ratio. Other than the randomization ratio, the methodology of the two stages of the study will be identical.

In the first stage of the study, approximately 300 subjects will be enrolled to receive either one dose of Chiron MenACWY Conjugate Vaccine with adjuvant or one dose of the licensed control vaccine (Menomune®). The second stage will enroll approximately 190 subjects to receive either one dose of Chiron MenACWY Conjugate Vaccine without adjuvant or one dose of the licensed control vaccine (Menomune®). Enrollment in Stage 2 will commence after enrollment in Stage 1 has been completed. The total number enrolled receiving each of the study vaccines will be approximately:

Group 1: Chiron MenACWY Conjugate Vaccine with adjuvant	150
Group 2: Menomune®	188
Group 3: Chiron MenACWY Conjugate Vaccine without adjuvant	152

6.3 Selection of Study Population

Healthy subjects who meet the following inclusion criteria and none of the exclusion criteria will be eligible for the study.

6.3.1 Inclusion Criteria

Individuals meeting all of the following criteria will be eligible for enrollment into the study:

Adolescents (male and female)

1. who are between 11 and 17 years of age inclusive and are available for all visits and telephone calls scheduled for the study;

2. who have given written assent and/or for whom the parent or legal guardian has provided written informed consent after the nature of the study has been explained;

3. who are in good health as determined by:

    - medical history
    - physical examination
    - clinical judgment of the investigator

Informed consent and assent must be obtained for all the subjects before enrollment in the study.

6.3.2 Exclusion Criteria

Adolescents not eligible to be enrolled in the study are those:

1. who or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;

2. who had a previous suspected disease caused by *N meningitidis*;

3. who had household contact with and/or intimate exposure to an individual with culture proven *N meningitidis* serogroup A, C, W, and/or Y infection within 60 days prior to enrollment;

4. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational);

5. who have received any investigational agents or vaccines 90 days prior to enrollment;

6. who have received any licensed vaccines within the 30 days prior to enrollment or for whom receipt of a licensed vaccine is anticipated within the 30 days after immunization. (Exception: Influenza vaccine may be administered 15 days prior to study immunization and 15 days after study immunization);

7. who plan to receive the recommended vaccines such as Td/Hep B series, MMR, Varicella, or Hep A series between Visit 1 and Visit 2. (Recommended vaccines for this age group may be administered after the blood draw at Visit 2);

8. with any serious acute illness;

9. who are pregnant or nursing (breastfeeding) mothers or females of childbearing age who have not used or do not plan to use acceptable birth control measures, as determined by the investigator for the 12-month duration of the study. Abstinence is considered an acceptable form of contraception. (Females will have a urine pregnancy test sensitive to 20 IU β-hCG at entry);

10. with any serious chronic or progressive disease (e.g., any history of neoplasm, insulin dependent diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring chronic use of inhaled or systemic corticosteroids are not eligible for enrollment.);

11. with epilepsy or any progressive neurological disease;

12. with a history of any anaphylactic shock, pulmonary reactivity, urticaria, or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component;

13. with a known or suspected disease of the immune system, or those receiving immunosuppressive therapy, including use of any systemic corticosteroids, or those who have received blood, blood products, or a parenteral immunoglobulin preparation within 60 days prior to study enrollment;

14. who have taken systemic antibiotics (either oral or parenteral) within the previous 14 days (Exception: subjects who have received an oral or parenteral β-lactam antibiotic [examples: penicillin, amoxicillin, ceftriaxone, cefuroxime, cephalexin, etc.] may be enrolled 7 days after the last dose);

15. known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

16. with Down's syndrome or other known cytogenic disorders;

17. with an oral temperature of 38.0°C (100.4°F) or more within 3 days prior to study entry;

18. with any condition that, in the opinion of the investigators, might interfere with the evaluation of the study objectives.

Reason for delaying subsequent blood draws:
Development of any condition specified in the initial exclusion criterion 14 cited above.

6.3.3 Removal of Subjects From Therapy or Assessment

Subjects or their parents or legal guardians, where appropriate, can withdraw consent for participation in the study at any time without prejudice. The Investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. The Sponsor can also request the removal of a subject from the study.

The subject will be monitored after withdrawal, the cause of which will be recorded in detail on the Study Termination CRF and where appropriate, on the subject's medical records. Where the withdrawal of a subject resulted from an AE, this will be documented in accordance with the procedures in Section 6.5.4.3. Whenever possible, the tests and evaluations listed for the termination visit will be carried out. Subjects withdrawn from the study will not be replaced.

If a subject (or the subject's legal representative) withdraws consent but does not revoke the HIPAA authorization, Chiron will have full access to the subject's medical records, including termination visit information. If a subject (or a subject's legal representative) revokes only the HIPAA authorization, Chiron will have full access to all of the subject's medical records prior to the date and time of revocation.

6.4 Vaccines

6.4.1 Vaccines Administered

Stage 1: At Visit 1, subjects will be randomly assigned in a 1:1 ratio to one of the following groups:

Group 1:
Subjects will receive a single dose injection of Chiron Men ACWY Conjugate Vaccine with aluminum phosphate adjuvant administered IM in the left deltoid.

Group 2:
Subjects will receive a single dose injection of Menomune® administered SC in the left upper arm.

Stage 2: At Visit 1, subjects will be randomly assigned in a 4:1 ratio to one of the following groups:

Group 3:
Subjects will receive a single dose injection of Chiron Men ACWY Conjugate Vaccine without aluminum phosphate adjuvant administered IM in the left deltoid.

Group 2:
Subjects will receive a single dose injection of Menomune® administered SC in the left upper arm.

6.4.2 Identity of Investigational Vaccine

6.4.2.1 Vaccine Composition

Chiron Men ACWY Conjugate Vaccine

The investigational Chiron Men ACWY Conjugate Vaccine is obtained by extemporaneously mixing the lyophilized Men A component to be re-suspended with the Men CWY component. The vaccine should be prepared just prior to administration to the study subject. The vaccine will have the following composition after reconstitution per 0.5 mL of injectable suspension:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Aluminum phosphate†	0.3 mg Al^{3+}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
(b) (4)	(b) (4)
WFI	(b) (4)

†Formulation without adjuvant identical except aluminum phosphate is not present

The Chiron Men ACWY Conjugate Vaccine consists of two vials:

One vial contains a lyophilized powder of meningococcal serogroup A oligosaccharides conjugated to *Corynebacterium diphtheriae* CRM_{197} protein.

One vial contains a solution of meningococcal serogroup C, Wand Y oligosaccharides conjugated to *Corynebacterium diphtheriae* CRM_{197} protein, with aluminum phosphate ($AlPO_4$) as an adjuvant.

The contents of the lyophilized Men A conjugate component are to be reconstituted with 0.6 mL of the content of the liquid Men CWY conjugate component to administer 0.5 mL of Men ACWY Conjugate Vaccine.

Menomune® – A/C/Y/W-135

Menomune® (manufactured by Aventis Pasteur Inc. Swiftwater, PA) consists of four meningococcal capsular polysaccharide serogroups (A, C, Y and W-135). After reconstitution, Menomune® will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
Isolated product from each of groups A, C, Y, and W-135	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: WFI	Qs to 0.5 mL

One 0.5 mL dose of Menomune® will be administered subcutaneously in the left upper arm.

Menomune® is packaged as two vials: one vial containing a single dose of lyophilized Men A, C, Y, and W-135 combined component and the second vial containing the diluent. The contents of the lyophilized Menomune® vial are to be reconstituted with the diluent.

6.4.2.2 Vaccine Labeling, Storage and Packaging

All vaccine supplies must be stored between 2 and 8ºC (36 to 46ºF). Do not freeze. In the event that vaccine supply has been subjected to different storage conditions than specified above, the study vaccine must not be used (unless the Sponsor provides written authorization for use). In the event that the use cannot be authorized, vaccine supply will be replaced.

The Sponsor will supply the investigational and comparator vaccines. The Investigator (or pharmacist) will make an inventory and acknowledge receipt of all shipments of study vaccine. All vaccines are to be stored in accordance with the instructions of the manufacturer.

Chiron Men ACWY Conjugate Vaccine

Chiron Men ACWY Conjugate Vaccine will be supplied and packaged as a single dose per carton. One carton will contain two vials: one vial will contain the lyophilized powder of the Men A component and the second vial will contain the liquid solution of the Men CWY component.

For each study vaccine, the carton label and the two vial labels will include a unique, blinded kit number, required storage conditions, sponsor name and location, and the appropriate cautionary statement. The carton label will include individual tear-off sections to attach to the syringe, case report form, and drug accountability log.

In the event that any of the vaccine dosing units is damaged, unusable, or has been stored or exposed to temperatures outside the permitted range, a replacement set (as appropriate to randomization) should be used.

Menomune® – A/C/Y/W-135

The Menomune® vaccine will be supplied and packaged as a single dose per carton. One carton will contain two vials: one vial containing a single dose of lyophilized Men A, C, Y, and W-135 combined component and the other vial containing the diluent.

The carton label will include a unique, blinded kit number, required storage conditions, sponsor name and location, and the appropriate cautionary statement. The carton label will include individual tear-off sections to attach to the syringe, case report form, and the drug accountability log. The commercial vial labels for Menomune® will remain intact.

6.4.2.3 Vaccine Administration

The Investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function.

Following reconstitution, the vaccine must be gently shaken and visually inspected before use.

Intravascular injections must not be given. Any fever or severe active infection is reason for delaying vaccination.

Directions for reconstitution and administration of Chiron Men ACWY Conjugate Vaccine (either with or without adjuvant):

At Visit 1, subjects randomized to Group 1 will receive a single dose injection of Men ACWY Conjugate Vaccine. The lyophilized Chiron Men A component requires preparation by reconstitution with the Chiron Men CWY full liquid component:

- Gently agitate the Men CWY full liquid component vial;
- Draw up 0.6 mL of Men CWY into a suitable size syringe (i.e., 2 mL) and inject into the Men A lyophilized component vial to reconstitute;
- Gently shake the reconstituted vial until the Men A lyophilized powder is dissolved;
- Using a new suitable gauge needle, withdraw 0.5 mL of reconstituted product, ensuring no air bubbles are present;
- If any foreign particulate matter and/or variation of physical aspect is observed, discard the vaccine. If no particulate matter and/or variation of physical aspect is observed, inject 0.5 mL of the reconstituted vaccine IM into the left deltoid.

Directions for reconstitution and administration of Menomune® vaccine:

At Visit 1, subjects randomized to Group 2 will receive a single dose injection of Menomune®. Menomune® contains one vial of lyophilized Men A, C, Y, W vaccine and one vial of diluent.

- Draw up 0.6 mL of the liquid diluent into a suitable size syringe (i.e., 2 mL) and inject the contents into the vial containing the lyophilized vaccine;
- Shake the reconstituted vial until the lyophilized Menomune® vaccine is dissolved;
- Using a new suitable gauge needle, withdraw 0.5 mL of reconstituted product, ensuring no air bubbles are present;
- If any foreign particulate matter and/or variation of physical aspect is observed, discard the vaccine. If no particulate matter and/or variation of physical aspect is observed, inject 0.5 mL of the reconstituted vaccine SC into the left upper arm.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines or to any substance contained in the vaccine. Any oral temperature ≥ 38°C (100.4° F) or severe infection is reason for delaying vaccination.

Standard immunization practices should be observed and care should be taken to administer the injections. As with any parenteral vaccine, epinephrine 1:1000 and systemic steroids should be available for immediate use should any anaphylactic reaction occur. Men ACWY study vaccine should be injected deep intramuscularly. **DO NOT inject intravascularly.**

6.4.3 Method of Assigning Subjects to Vaccination Groups

Subjects who meet the initial study inclusion criteria and no exclusion criteria will be assigned a six-digit number at Visit 1. The first two digits correspond to the site number (01) followed by a one-digit number that identifies the sub-site (2) and the last three digits correspond to the subject number (001).

In the first stage of the study, the Chiron Men ACWY vaccine and Menomune® vaccine will be assigned in a 1:1 randomization ratio within each site. In the second stage of the study, Men ACWY and Menomune® will be assigned in a 4:1 ratio. The randomization lists will be generated by the Chiron Biostatistics and Clinical Data Management (BCDM) group.

6.4.4 Selection of Doses in the Study

The doses used in this study are based upon dose and formulation finding studies conducted in toddlers in Finland, Germany and the United States. In one trial (Finland and Germany), more than 500 toddlers received at least one dose of one of 5 formulations of the Chiron Men ACWY Conjugate Vaccine (approximately 100 subjects per group). While all formulations were well tolerated and immunogenic, the formulation used in this trial appeared to provide optimal responses for Serogroup A relative to all other formulations.

In another trial conducted in the US, 235 toddlers received one dose of three formulations of investigational ACWY conjugate vaccine; two formulations without adjuvant at a fixed dose of 5 µg or 10 µg per oligosaccharide antigen and one formulation of 5 µg per oligosaccharide adjuvant with aluminum phosphate adjuvant. Although preliminary data suggest improved immunogenicity for at least one vaccine antigen component (W) in the presence of adjuvant, this trial will add further data to understand its relative contribution. For additional information on the design of these toddler studies, please see the Investigator's Brochure.

6.4.5 Blinding

The trial is designed as a single-blind study. Study subjects will be blinded to the vaccine to be administered. During the study, designated nurse(s) or physician(s) who are responsible for administering the study vaccines to the subjects, will be instructed not to reveal the identity of the study vaccines to the subjects or to the blinded study site personnel assessing the subjects. The unblinded site personel will maintain the study

vaccine codes in a secure location separate from the individual subject files restricting access to the blinded site personnel. Study vaccine codes will not be available to the blinded site personnel or to Chiron personnel monitoring the trial until after the completion of the trial and final data review.

6.4.6 Prior and Concomitant Therapy

No concomitant vaccines will be administered from enrollment to Visit 2.

Normal routine or catch-up immunizations appropriate for this age group (e.g., vaccines to prevent diphtheria, tetanus, pertussis, hepatitis A, hepatitis B, measles, mumps, rubella, pneumococcal infection, polio, varicella), or other recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria (i.e., vaccines to prevent influenza, pneumococcal infection), may be administered after the blood draw at Visit 2. *(Exception: Influenza vaccine may be administered 15 days prior to study immunization and 15 days after study immunization).*

All prescription medications and non-prescription medications should be recorded on the Concomitant Medications CRF for the first 7 days after vaccination. Concomitant use of the following medications at any time during the study is discouraged:

a. corticosteroids in doses known to be associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis (i.e., systemic corticosteroids) or chronic use of inhaled high-potency corticosteroids;
b. blood, blood products, or a parenteral immunoglobulin preparation;
c. other immunosuppressive agents.

If antipyretics/analgesics are given on the day of vaccination or for treatment of fever, the temperature should be retaken and recorded 4 hours after the antipyretic dose to see if further treatment is necessary. This information must be recorded in the subject diary and on the appropriate CRF pages.

6.4.7 Vaccination Compliance

The Investigator will be responsible for adequate and accurate accounting of vaccine usage. The unblinded site personnel will prepare and administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage and time of the vaccinations will be recorded. The unblinded site personnel will track vaccines received, used and wasted and will retain all unused or expired products until the Sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be returned to the Sponsor or destroyed at the investigational site according to the relevant Chiron SOP. An overall summary of vaccines supplied, received, wasted, used, and returned will be prepared at the conclusion of the study.

6.4.8 Adherence to Randomization List

Adherence to randomization list will be verified by a designated and unblinded Study Monitor by checking the randomization list against the vaccination records maintained at the study site.

6.5 Immunogenicity and Safety Measurements and Variables

6.5.1 Immunogenicity and Safety Measurements

MEASURES OF IMMUNOGENICITY:

The ability of Men ACWY Conjugate Vaccine to elicit functional serum bactericidal activity (SBA) against each serogroup in the presence of human complement (hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed (e.g. ELISA).

MEASURES OF SAFETY:

The measures of safety to be used in this study consist of local and systemic reactions and other adverse events.

The assessment of local reactions will include: pain, erythema, and induration. The assessment of systemic reactions will include: chills, nausea, malaise, myalgia, arthralgia, and headache.

6.5.2 Appropriateness of Measurements

The safety measures used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response). The measures of safety used in this study are routine clinical and laboratory procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic reactions routinely monitored in vaccine clinical trials as indicators of reactogenicity.

6.5.3 Immunogenicity and Safety Variables

6.5.3.1 Immunogenicity Variables

For each serogroup, hSBA will be measured and expressed as GMT and percent of subjects with hSBA response (i.e., % $\geq$ 1:4). Additional analyses may be performed to further describe the bactericidal response (e.g., % $\geq$ 1:8).

The analysis will be done at the Chiron Vaccines Clinical Serology laboratory in Marburg, Germany.

6.5.3.2 Safety Variables

A medical history will be obtained and physical examination performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected. Safety will be assessed in terms of the number of subjects with reported local and systemic reactions and/or all AEs through Day 7 and/or all SAEs and/or AEs requiring a physician visit and/or resulting in premature withdrawal from the study, per vaccination group through study termination.

ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

The severity of events reported on the Adverse Events CRF will be determined by the Investigator as:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the Investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational vaccine has not occurred, OR the occurrence of the AE is not reasonably related in time, OR the AE is considered unlikely

to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time AND the AE could be explained by causes other than exposure to the investigational vaccine.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time AND the investigational vaccine is more likely than other causes to be responsible for the AE, OR is the most likely cause of the AE.

The period of observation and reporting of adverse events extends from the time the subject gives informed consent until he or she undergoes the final study examination. This may include a period before and after an active treatment of an investigational product (study vaccine) or other medication. All subjects experiencing adverse events, regardless of severity and whether considered associated with the use of the study vaccine or not, must be monitored by the Investigator until symptoms subside and any abnormal laboratory values have returned to baseline, the AE is determined to be chronic, a cause is identified, or until there is a satisfactory explanation for the changes observed. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and Medical Monitor whether continued follow-up of the AE is warranted.

The following are the documentation requirements of adverse events during the different timepoints of the study. From Day 1 through Day 7, record and collect information regarding **all** adverse events. From Day 8 up to Visit 2 (Day 29), record and collect information regarding any SAE, any event requiring a medical office visit, and any event resulting in a subject's early termination. From Visit 2 through Visit 3, record and collect any SAE, any significant medical event, and any event resulting in a subject's early termination.

All adverse events must be reported in the subject's medical records and on an "Adverse Events" CRF and, if appropriate, on the "Vaccine Serious Adverse Event" form. All adverse events must be reported and documented according to 21 CFR 312.32, and as specified in section 6.5.4 Study Procedures and Time and Events Table of the protocol, and the Manual of Operations for this study.

Post-study events

Any adverse event occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine — and therefore a possible adverse drug reaction — must be reported.

SERIOUS ADVERSE EVENT

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions);
- Results in a congenital anomaly/birth defect;
- Requires intervention to prevent permanent impairment or damage;
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Of note: a "possible vaccine failure" should be reported as an SAE only if it resulted in an infectious disease which should have been prevented by the vaccine implied.

Adverse events that do not fall into these categories are defined as **non-serious**.

It should be noted that an SAE need not be serious in nature and that an SAE need not, by definition, be severe.

All SAEs that occur during the course of the trial, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following Chiron personnel.

Medical Monitor: Peter Dull, MD
Phone number: (510) 923-3192
FAX number: (510) 923-3450

Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916

Study Monitor: Bridget Waluch
Phone number: (510) 923-3161
FAX number: (510) 923-3450

Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916

Serious Adverse Event 24-hour telephone number: (510) 502-3650

The Investigator will report SAEs to the IRB, IEC, or any relevant authorities in accordance with the standard operating procedures and policies of the IRB, IEC, or authorities. Adequate documentation must be provided to Chiron showing that the IRB or IEC was properly notified.

Refer to the Manual of Operations for this study for detailed instructions on documenting SAEs and completion and submission of the Vaccines Serious Adverse Event form.

LOCAL AND SYSTEMIC POSTIMMUNIZATION REACTIONS

Postimmunization Events Monitored as Possible Reactions to Vaccine

Selected local and systemic adverse events are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within a specified period of time after immunization are herein termed "postimmunization reactions".

Instructions to Parent/Legal Guardian Regarding Unusual or Severe Signs or Symptoms

Parents or legal guardians will be instructed to call the specified study personnel immediately if any unusual or severe sign or symptom appears after immunization. Subjects who experience severe systemic reactions should be seen in the clinic at the time of maximal symptoms, if possible. Subjects will be followed clinically until resolution of symptoms.

In addition to postimmunization reactions, subjects will also be evaluated for other adverse events at 30 minutes after each study vaccination and at the subsequent clinic visits. Subjects and/or their parents/legal guardians will be instructed to report any other adverse events that may be of concern to them to the study personnel during the telephone interviews at 3 days and 180 days after study vaccination, and at the scheduled study visits.

Local reactions:

pain, erythema, and induration

Systemic reactions:

chills, nausea, malaise, myalgia, arthralgia, and headache

6.5.4 Study Procedures and Time and Events Table

6.5.4.1 Study Procedures

Visit 1. Study Day 1: Screening/Baseline and Vaccination

Pre-study Screening

All screening must occur at Visit 1 before vaccination.

a. Explain and obtain written informed consent and assent from the subject and the subject's parent/legal guardian. Written informed consent and assent must be obtained prior to performance of any study-specific tests or evaluations.

b. Obtain and record medical history.

c. Perform a physical examination/assessment including measurement of oral temperature, weight and height, and a check of general appearance, and systems evaluation. A urine pregnancy test will be conducted for females of childbearing potential. The physical examination should be performed by the investigator or designate of the investigator.

d. If the subject continues to meet all inclusion and no exclusion criteria, assign the subject number in ascending order.

e. Obtain blood sample via venipuncture (20 mL) from all subjects enrolled. Process blood and store serum for serologic evaluation.

f. The unblinded site personnel will administer the study vaccine, according to the randomization instructions.

g. Examine the injection site of the vaccine for local reactions at the end of 30 minutes. Record these findings and any systemic reaction on the appropriate CRF. Enter findings from the 30-minute post-injection evaluation onto the subject diary card.

h. Instruct the subject and parent/legal guardian in the evaluation of local and systemic reactions, and recording of oral temperature.

i. From Day 1 through Day 7, record and collect **all AEs** whether considered associated or not associated with the use of the study vaccine. Record adverse events other than local injection site reactions and systemic reactions on the Adverse Events CRF.

j. Dispense subject diary card for vaccination reactions, and give subject and parent or legal guardian instructions for its completion. Give subject or parent/ legal guardian a digital thermometer and a ruler and instruct them in their use.

k. Schedule subject to return for Visit 2.

Study Day 3. Telephone Contact: 2 to 4 Days after Study Visit 1

The subject or parent/legal guardian of the subject will be contacted by telephone by study site personnel 2 days after vaccination (Study Day 3) to remind the subject or parent/legal guardian to record reaction data, any other medical problems, and use of concomitant medication on the Diary Card. Record any medical problems reported by the subject and/or parent/legal guardian that is of concern.

Visit 2. Study Day 29: 28 to 35 Days after Study Visit 1

a. Perform a physical examination/assessment, including measurement of oral temperature and examination of previous injection site. Any new adverse findings must be recorded onto the appropriate CRFs.

b. Collect the diary card and review with the subject and/or parent/legal guardian. Reconcile any outstanding medical problems identified during the telephone contact conducted at Day 3. Record and collect information regarding any SAE, any event requiring a medical office visit, or any event resulting in a subject's early termination reported from Day 8 through Visit 2.

c. Collect prescription medications used to treat reported adverse events. Record information obtained on the appropriate CRFs.

d. Obtain blood sample via venipuncture (20 mL). Process blood and store serum for serologic evaluation.

e. Dispense subject vaccination worksheet and give subject or parent/legal guardian instructions for its completion.

f. Remind subject and parent/legal guardian that they will be contacted by phone in 5 months.

Study Day 180. Telephone Contact: 164 to 194 Days after Study Visit 1

The subject or parent/legal guardian will be contacted by the investigator or designee from 164 to 194 days after vaccination to obtain any SAEs, any significant medical events, or any event resulting in a subject's early termination.

Visit 3. Study Day 360: Study Termination: 344 to 374 Days after Study Visit 1

a. Perform brief physical examination/assessment, including measurement of oral temperature and examination of previous injection site. Any new adverse findings must be recorded onto the appropriate CRFs.

b. Review and collect the worksheet and review with the subject and/or parent/legal guardian. Reconcile any outstanding issues identified during the telephone contact conducted at Day 180.

c. Record and collect any information regarding any SAEs, any significant medical events, or any events resulting in a subject's early termination reported from Visit 2 through Visit 3.

d. Collect prescription medications used to treat reported adverse events. Record information obtained on the appropriate CRFs.

e. Obtain blood sample via venipuncture (20 mL). Process blood and store serum for serologic evaluation.

Early Withdrawal Evaluation

The study staff should attempt to contact the subject and/or the subject's parent/legal guardian. The final attempt should include mailing a certified letter to the subject's last known address. If possible the subject should return to the clinic for a Study Termination evaluation visit.

6.5.4.2 Time and Events Table

Visit Number **Study Day**	1 1	☎ 3	2 29	☎ 180	3 360
(Range)	(1)	(2 to 4 days after Visit 1)	(28 to 35 days after Visit 1)	(164 to 194 days after Visit 1)	(344 to 374 days after Visit 1)
Procedures					
Obtain Informed Consent	x				
Medical History	x				
Physical Examination[a]	x		x		x
Obtain Blood Sample	x		x		x
Administer Study Vaccine[b]	x				
Injection-site Examination[c]	x		x		x
Assess Local and Systemic Reactions[d]	x		x		
Concomitant Medications	x[e]	x[e]	x[f]		x[f]
Adverse Events[g]	x	x	x	x	x
Study Termination					x

Note: Day 1 is defined as day of study vaccination.

[a] The physical examinations at Visits 1, 2 and 3 (Study Days 1, 29 and 360) should be performed by a study physician or a designated study nurse.

[b] The study vaccine, Chiron Men ACWY Conjugate Vaccine, will be administered IM into the subjects left deltoid or a licensed meningococcal vaccine, Menomune®, will be administered SC into the subject's left upper arm. All subjects will be observed in the clinic for 30 minutes after vaccination.

[c] Inspect the injection site at all study visits.

[d] Local and systemic reactions following vaccination will be noted by subjects in the diary cards daily for 7 days after vaccination (Study Days 1 through 7). The diary cards will be reviewed during the Day 3 follow-up phone interview and collected at Visit 2.

[e] Collect data on concomitant medications (prescription and non prescription) through the first 7 days.

[f] Collect data on concomitant medications (prescriptions only) from Day 8 through Visit 3.

[g] From Day 1 through Day 7, record and collect information regarding **all AEs**. From Day 8 up to Visit 2, record and collect information regarding any SAE, any event requiring a medical office visit, and any event resulting in a subject's early termination. From Visit 2 through Visit 3, record and collect any SAE, any significant medical event, and any event resulting in a subject's early termination.

6.5.4.3 Laboratory Assessments

There will be no clinical laboratory tests performed during this study. Pregnancy tests at the study entry will be read and documented by site personnel.

Immunogenicity of the study vaccines will be evaluated by the Chiron Vaccines Clinical Serology laboratory in Marburg, Germany for the presence of bactericidal antibodies to *N meningitidis* serogroups A, C, W-135, and Y (b) (4) Additional tests may be performed (e.g., ELISA for the presence of IgG antibodies to *N meningitidis* serogroups A, C, W-135, Y capsular polysaccharide). Please refer to the Manual of Operations for instructions on serum processing, storage and shipment.

Blood samples taken in the following time windows will be evaluable:

Pre-vaccination:	Day 1
Post-vaccination:	Day 29 (window: 28 to 35 days post-vaccination)
Post-vaccination:	Day 360 (window: 344 to 374 days post-vaccination)

6.5.4.3.1 Labeling and Storage of Serum Samples

At the estimated time-points, perform phlebotomy and collect 20 mL of whole blood.

The blood will be centrifuged on the same day and serum will be distributed in four aliquots using the tubes provided.

The aliquots will be stored at a temperature of minus 18°C or below.

Each serum tube will be labeled with an identifying bar code including site, subject and protocol number. Serum samples will be sent to the Sponsor laboratory at the address specified below:

Chiron Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg, Germany
Phone: 011 49 6421 39 3439/3712

Complete instructions for labeling and storage of serum samples are included in the V59P6 Manual of Operations.

6.6 Study Monitoring, Auditing and Documentation

Investigators and/or their personnel will be trained before and at least during the initiation visit. During each monitoring visit source data verification will be performed by qualified

staff representing the Sponsor. A CRF collation supplied by the Sponsor will be completed for each subject. The entries will be checked by trained delegates of the Sponsor.

Monitoring and auditing procedures of the Sponsor will be followed, in order to comply with ICH GCP guidelines and to ensure validity of the study data.

The Sponsor's Clinical Quality Assurance department will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with ICH GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms, the Analysis Plan and the Subject Information and Consent Form.

6.6.1 Study Monitoring

The clinical study site will be monitored by regular site visits and telephone calls to the Investigator by members of the Chiron Clinical Research Department or their agents following Chiron's internal standard operating procedure. CRFs and all original data collected at the site including subjects' medical records and drug accountability records should be available for review during monitoring visits.

6.6.2 Source Data Verification and Audits

Inspection and examination of CRFs and source documents (all original recordings, laboratory reports, medical records) giving due consideration to data protection and medical confidentiality will be undertaken by representatives of the Sponsor. All data not recorded directly on the CRFs as defined in section 6.10 of this study protocol must be verified by checking CRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol. Source data verification will be performed and recorded following Chiron internal standard operating procedure. The subject or the subject's legal representative must also allow access to the subject's medical records. Each subject will be informed of this prior to the start of the study.

During or after the clinical study, the regulatory authorities, the EC/IRB, Food and Drug Administration (FDA) and/or representatives of the Sponsor may request access to all source documents, CRFs and other study documentation for on-site audit or inspection.

6.7 Data Management

All CRF data will be entered in duplicate into a (b) (4) database by BCDM, Chiron. Data validation will be performed using (b) (4) (a programming language) and (b) (4) (b) (4) Data quality assurance will be performed by doing a 100% check of all database updates resulting from the resolution of queries,

and by estimating the database error rate with 95% upper confidence limit. The latter must be below the departmental accepted level of 0.5%.

All serology data analyzed in Chiron Laboratories will be entered into the (b) (4) database by Clinical Serology, Chiron Vaccines, Marburg, Germany.

6.7.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

6.8 Changes in the Conduct of the Study or Planned Analysis

Changes in the conduct of the study will be described in protocol amendments; changes in the planned analysis will be described in the clinical study report.

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical Plans

Chiron will perform data analyses as defined in the Analysis Plan (AP). Tables, listings and graphs will be generated using (b) (4) version (b) (4)

The following populations will be analyzed:

<u>All Randomized Population:</u>

This population includes all subjects enrolled and randomized in the study, i.e. all subjects who have data in the demography dataset. This population will be used for analysis of demographics and all subject listings.

<u>Immunogenicity, Modified Intent-to-treat (MITT) Population</u>:

This population will include vaccinated subjects who: (a) have non-missing immunogenicity data at baseline; and (b) have non-missing immunogenicity data at a minimum of one visit postbaseline.

<u>Immunogenicity, Per Protocol (PP) Population:</u>

This population includes all subjects in the MITT population who have no major protocol deviations as defined in the AP.

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity (or efficacy) results of the subject. The major protocol deviations will be identified prior to the analysis (e.g., visit out of window, inclusion/exclusion criteria, forbidden concomitant medications). A clinical judgment may be used to classify each deviation as major or not.

The PP population will be considered the primary immunogenicity population. If there is a significant overlap in the PP and MITT populations, the immunogenicity analysis may be performed on only the PP population.

Safety Population:

All subjects who have received a study vaccine and have post-baseline safety data will be included in the safety analysis.

All data exclusions, including premature terminations, will be listed and tabulated according to vaccination group. Data listings will include all collected data.

The inclusion of covariates for immunogenicity analyses will be discussed in the AP. Two-sided p-values will be assessed for statistical significance at the 0.05 level.

Comparison of Baseline Characteristics:

Demographic and baseline data will be summarized for all randomized subjects to descriptively assess comparability of the vaccine groups at baseline.

Demographic and baseline data may be summarized for MITT and PP population as well.

6.9.1.1 Analysis of Immunogenicity Criteria

Primary Immunogenicity Analysis

The percent of responders is defined as the percent of subjects belonging to a given analysis population (e.g., the PP population) with hSBA titer ≥ 1:4.

The primary immunogenicity analysis is the comparison of the percent of responders in the two groups for each of the four components 1 month after vaccination. Comparisons will be based on the Chi-square test or Fisher's exact test as appropriate for expected cell counts. No adjustments in the Type I error rate will be made for the comparisons of the four components.

Secondary Immunogenicity Analysis

The hSBA GMTs 1 month and 12 months after vaccination will be evaluated in the two groups for each of the four components after log-transforming the titers. The comparison

of the means from each group of the log-transformed titers will be performed using a linear model that will also assess the effect of centers.

The percent of responders 12 months after vaccination will be evaluated in the two groups for each of the four components. Comparisons will be based on the Chi-square test or Fisher's exact test as appropriate for expected cell counts.

6.9.1.2 Analysis of Safety Criteria

Post-vaccination Reactions (Local and Systemic)

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

For the local and systemic reaction safety variables, differences among the vaccine groups after each scheduled vaccination and after any vaccination with respect to all variables (including fever) will be analyzed by using Pearson's chi-square test, or Fisher's Exact test where appropriate.

The power to detect differences between the two groups in rates of any one local or systemic reaction for sample sizes of 188 subjects receiving Menomune and 150 subjects receiving Men ACWY (either adjuvanted or unadjuvanted) is shown for varying rates in the table below. (b) (4) version (b) (4) was used to perform the calculations.

Percent of Menomune® subjects with any one local or systemic event (n=188)	Percent of Men ACWY subjects with any one local or systemic event (n=150)	Power (2-sided $\alpha = 0.05$)
5%	15%	86%
10%	20%	73%
10%	25%	95%
15%	25%	63%
15%	30%	91%
20%	30%	56%
20%	35%	87%

Other Adverse Events

All the AEs reported during the study, either judged as related to vaccination or not by the investigator, will be recorded.

The original verbatim terms used by investigators to identify AEs in the CRFs will be mapped to preferred terms using the MedDRA® dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). All reported AEs, as well as AEs at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) SAEs, (ii) AEs that are possibly or probably related to vaccine, and (iii) AEs that are unrelated to vaccine. Data listings of all AEs will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an AE will be presented.

6.9.1.3 Interim Analysis Planned

To facilitate the planning of future trials, before all subjects have completed Visit 2, a group unblinded interim analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization). The analyses will be governed by the procedures specified in the Chiron BCDM standard operating procedure entitled "Interim Analysis in a Clinical Trial."

6.9.1.4 Preliminary Analysis

A preliminary analysis may be performed to assess immunogenicity and 1-month safety (including local and systemic post-immunization reactions within 7 days of immunization) after all subjects have completed Visit 2.

6.9.2 Determination of Sample Size

The null hypothesis associated with the primary immunogenicity objective is that the proportion of subjects who are responders (i.e., hSBA titer ≥ 1:4) on Men ACWY is inferior to the proportion of subjects who are responders on Menomune® for the same serogroup. A given Men ACWY serogroup will be assessed to be non-inferior to that serogroup of Menomune® if the lower limit of the two-sided 95% confidence interval (CI) around the difference in proportions (Men ACWY *minus* Menomune®) is greater than -10%. This is equivalent to a one-sided 97.5% CI.

Power was calculated for various response rates as shown in the table below assuming that 175 Menomune subjects and 140 Chiron Men ACWY Conjugate Vaccine subjects (either adjuvanted or unadjuvanted) provide evaluable samples. The one-sided Type I error rate alpha was set equal to 0.025 and the percent of time the lower limit (LL) of the 95% CI for the difference in proportions (given serogroup for Men ACWY *minus* given serogroup for Menomune®) exceeded -10% was calculated. (b) (4) version (b) (4) was used to perform the calculations (random seed = 1732951, 20000 simulations).

Percent of responders in one serogroup of Menomune: P1 (n=175)	Percent of responders in one serogroup of Men ACWY: P2 (n=140)	Power that the LL exceeds -10% (1-sided $\alpha = 0.025$)
85%	83%	46%
85%	85%	67%
90%	87%	45%
90%	90%	80%
90%	95%	>99%
95%	95%	94%

6.10 Documentation of Study Findings

A set of CRF collations will be supplied by the Sponsor. The CRFs do not require carbon paper. The bottom copy must be retained by the Investigator, and all other copies will be returned as directed by the Sponsor. Instructions on how to complete these forms will be given to the Investigator.

All study findings must be entered by the Investigator on these CRFs. If the Investigator authorizes other persons to make entries on the CRF, the names, positions, signatures and initials of these persons must be supplied to the Sponsor.

All entries in the CRFs must be made legibly in black ballpoint pen (not pencil, felt tip or fountain pen).

For each enrolled subject a CRF collation must be signed and dated by the Investigator named in the study protocol. CRFs must be completed immediately after the final examination. Arrangements will be made by the monitor to collect the CRFs on completion. No CRFs are to be mailed to the Sponsor without specific authorization.

A reasonable explanation must be given by the Investigator for all missing data.

If corrections are made to entries in the CRF by the Investigator or designates, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made after review and signature by the Investigator, he/she must be made aware of the changes and document this awareness. Refer to the Manual of Operations for this study for detailed instructions on CRF completion and the data clarification process.

6.11 Record Retention

The Investigator(s) must retain records required by the Sponsor and by the applicable regulatory regulations in a secure and safe facility. The Investigator must consult a Sponsor's monitor before disposal of any study records, and must notify the Sponsor of any change in the location, disposition or custody of the study files. The period of record retention should be consistent with the record retention policies of the country where the study is being conducted.

The ICH GCP guideline requires retention for 2 years following the last date a marketing application is approved, in an ICH region these documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Committee for Proprietary Medicinal Products (CPMP) in Europe requires retention for the maximum period of time permitted by the institution, but not less than 15 years. Records must be retained for a period at least as long as that specified by FDA regulations. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by an agreement with the Sponsor.

The Sponsor requests that the Investigator arranges for the retention of CRFs, source records, and other supporting documentation for a minimum of 15 years.

6.12 Instructions for Study Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects.

The Ethics Committee/Institutional Review Board must be informed of all amendments and if necessary prior review and documented approval/favorable opinion must be sought for ethical aspects. Approval must also be obtained from the authorities if necessary.

Such amendment will be agreed upon by the Sponsor, the Investigator, and the Ethics Committee/Institutional Review Board prior to implementation.

An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes).

Any revision of the protocol (amendments and administrative changes) will be integrated in an updated study protocol.

6.13 Use of Information and Publication

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement between Chiron and the Investigator.

7 SIGNATURE PAGE

Study Title: A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with or without Aluminum Phosphate Adjuvant with the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

Study Number: V59P6 – Amendment 1

I have read the foregoing protocol and agree to conduct the study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____

Investigator Signature Date

Print name:_____

On behalf of Chiron, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this study.

_____ _____

Medical Monitor Signature Date

Print name:_____

9 REFERENCE LIST

1. Andersen BM. Mortality in meningococcal infections. Scand J Infect Dis 1978;10:277-82.
2. De Wals P, Hertoghe L, Reginster G, Borlee I, Bouckaert A, Dachy A, et al. Mortality in meningococcal disease in Belgium. J Infect 1984;8(3):264-73.
3. Halstensen A, Pedersen SH, Haneberg B, Bjorvatn B, Solberg CO. Case fatality of meningococcal disease in western Norway. Scand J Infect Dis 1987;19(1):35-42.
4. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81(4):536-8.
5. Campagne G, Chippaux JP, Djibo S, Issa O, Garba A. [Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger)]. Bull Soc Pathol Exot 1999;92(2):118-22.
6. Centers for Disease Control and Prevention. Laboratory-based surveillance for meningococcal disease in selected areas--United States, 1989-1991. Morbidity Mortality Weekly Report (MMWR); CDC Surveillance Summaries 1993;42 (SS-2):21-30.
7. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Carter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894-1901.
8. Ramsay M, Kaczmarski E, Rush M, Mallard R, Farrington P, White J. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev 1997;7(4):R49-54.
9. Decosas J, Koama JB. Chronicle of an outbreak foretold: meningococcal meningitis W135 in Burkina Faso. Lancet Infect Dis 2002;2(12):763-5.
10. Taha MK, Parent Du Chatelet I, Schlumberger M, Sanou I, Djibo S, de Chabalier F, et al. *Neisseria meningitidis* serogroups W135 and A were equally prevalent among meningitis cases occurring at the end of the 2001 epidemics in Burkina Faso and Niger. J Clin Microbiol 2002;40(3):1083-4.
11. du Chatelet IP, Alonso JM, Taha MK. [Clonal expansion of *Neisseria meningitidis* W135. Epidemiological implications for the African meningitis belt]. Bull Soc Pathol Exot 2002;95(5):323-4; discussion 324-5.
12. Rosenstein N, Fischer M, Tappero JW. Meningococcal Vaccines. Infectious Disease Clinics of North America 2001;15(1):155-169.
13. Centers for Disease Control and Prevention. Meningococcal disease and college students: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2000;49(RR-7):13-20.
14. Cadoz M, Armand J, Arminjon F, Gire R, Lafaix C. Tetravalent (A, C, Y, W 135) meningococcal vaccine in children: immunogenicity and safety. Vaccine 1985;3(3):340-342.

15. King WJ, MacDonald NE, Wells G, Huang J, Allen U, Chan F, et al. Total and functional antibody response to a quadrivalent meningococcal polysaccharide vaccine among children. Journal of Pediatrics 1996;128(2):196-202.
16. Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. Pediatrics 1977;60(5):673-680.
17. Reingold AL, Hightower AW, Bolan GA, Jones EE, Tiendrebeogo H, Broome CV, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet 1985;2(July 20, 1985):114-118.
18. Käyhty H, Mäkelä PH, Peltola H. Immunological basis for PRP vaccines. In: Ellis RW, Granoff DM, editors. Development and Clinical Uses of Haemophilus b Conjugate Vaccines. New York, NY: Marcel Dekker Inc.; 1994. p. 1-18.
19. Rosenstein N, Perkins B. Update on *Haemophilus influenzae* serotype b and meningococcal vaccines. Pediatr Clin North Am 2000;47(2):337-352, vi.

CLINICAL STUDY PROTOCOL V59P11
Final issued 28 November 2005
Amendment N° 1, issued 27 June 2006
Amendment N° 2, issued 05 July 2006
Amendment N° 3, issued 17 April 2007

Version number	4	**Eudract number**	2005-005519-12
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A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria, and Acellular Pertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, Or One Dose of Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, in Healthy Subjects Aged 11-25 Years

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STUDY SYNOPSIS

TITLE OF STUDY:

A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria and Acellular Pertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, Or One Dose of Novartis (formerly Chiron**)** Meningococcal ACWY Conjugate Vaccine in Healthy Subjects Aged 11-25 Years

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STUDY PERIOD
Approximately 12 months overall:
6 months of enrollment and 6 months of individual subject participation

CLINICAL PHASE:
Phase 3

RATIONALE:

Neisseria meningitidis causes life threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified, with serogroups A, B, C, W135 and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. Licensed tetravalent polysaccharide vaccines against serogroup A, C, W135 and Y have been available for many years and are widely used. However they do not provide long-term protection and are poorly immunogenic, even in the short-term, in children below 2 years of age.

Based upon the recent, successful development of conjugate vaccines designed to prevent disease caused by *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* serogroup C, Novartis (formerly Chiron) is developing a conjugate Men ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM197 (a non-toxic mutant of diphtheria toxin).

An FDA panel recently recommended approval of Tdap booster targeting >11 years old. US based analysis for use in adolescents projected that vaccination of people aged 10-19 during a 10-year period would prevent up to 1.8 million cases of pertussis. According to the CDC, there were almost 20,000 cases of pertussis in 2004 – the highest number of reported cases in more than 40 years. In addition, 39% of cases reported to the CDC in 2003 occurred in adolescents 10-19 years of age. Adolescents, in whom classic signs and symptoms of pertussis are often absent, may go undiagnosed and be the source of infection for susceptible infants and other family members.

The main objective of the proposed phase 3 study is to describe and compare the immunogenicity profile of a single dose of Novartis (formerly Chiron) Men ACWY administered alone or concomitantly with a licensed combined Tdap vaccine (Boostrix®, GSK), with that of a single dose of Tdap, when administered to healthy adolescents and young adults 11-25 years of age.

Novartis (formerly Chiron) Men ACWY conjugate vaccine has already been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 1400 subjects (from infants up to 17 years old) have received at least one dose of the formulation of Novartis (formerly Chiron) Men ACWY conjugate vaccine being tested in this study. A comprehensive and detailed review of investigational Novartis (formerly Chiron) Men ACWY conjugate vaccine is contained in the Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

OBJECTIVES:

Immunogenicity Objectives

Primary

To demonstrate that the immunogenicity of a single dose of Tdap vaccine, separately but concomitantly administered with Novartis (formerly Chiron) MenACWY, is not inferior to that of a single dose of Tdap vaccine, concomitantly administered with a saline placebo.

Secondary

- To compare the immunogenicity of a single dose of Tdap vaccine when given separately but concomitantly administered with Novartis MenACWY, to that of a single dose of Tdap vaccine, concomitantly administered with a saline placebo. Immunogenicity response of Tdap is defined as: 1) percentage of subjects with ELISA anti-diphtheria toxin ≥ 0.1 IU/mL and anti-tetanus toxin ≥ 0.1 IU/mL at one month after vaccination; 2) anti-diphtheria, anti-tetanus, anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), and anti-pertactin (anti-PRN) ELISA geometric mean concentration (GMC) at baseline and at one month after vaccination, and GMC increase (geometric mean ratio, GMR) from baseline at one month after vaccination.

- To evaluate the immunogenicity of a single dose of Novartis MenACWY vaccine, separately but concomitantly administered with Tdap, and that of a single dose of Novartis MenACWY vaccine, concomitantly administered with a saline placebo. Immunogenicity response of Novartis MenACWY is defined as: 1) percentage of subjects with hSBA seroresponse; 2) percentage of subjects with hSBA ≥ 1:4 and percentage of subjects with hSBA ≥ 1:8 at one month after vaccination; 3) hSBA geometric mean titer (GMT) at baseline and at one month after vaccination, and GMT increase (GMR) from baseline at one month after vaccination.

Safety Objectives

To describe and compare the safety profile following a single dose of Novartis (formerly Chiron) Men ACWY + Tdap vaccines to that of either Tdap + saline placebo or Novartis (formerly Chiron) Men ACWY + saline placebo when administered to healthy subjects 11-25 years of age, defined as percentage and number of subjects with:

- Immediate hypersensitivity reactions following vaccination
- Local and systemic reactions and axillary temperature reported during the period Day 1 - Day 7 after vaccination

- Adverse events (AEs) reported during the period Day 1 - Day 29 after vaccination
- Medically significant AEs reported during the period Day 30 - Day 181 after vaccination
- Serious adverse events (SAEs) reported for the whole duration of the study

METHODS:

This a phase 3, observer-blind, multi-center, randomized, controlled study in healthy subjects aged 11-25 years.

Subjects will be included in the study if in good health as judged by physical examination and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 1000 healthy subjects aged 11-25 years will be randomized in a 1:1:1 ratio to receive either concomitant administrations of Tdap + Novartis (formerly Chiron) Men ACWY vaccines (Group I), or Tdap vaccine + saline placebo (Group II), or Novartis (formerly Chiron) Men ACWY + saline placebo (Group III).

At Visit 1 (Day 1), prior to administration of study vaccine, a blood sample (10 mL) will be obtained for serologic evaluation. Post vaccination blood sample (10 mL) will be collected at Visit 2 (Day 29).

Group (N)	**Day 1 Visit 1**	**Day 29 Visit 2**
I (333)	Serology Tdap + Men ACWY	Serology
II (333)	Serology Tdap + saline	Serology
III (333)	Serology Men ACWY + saline	Serology

At the enrollment visit (Visit 1), the investigator, or a person designated by the investigator, should fully inform the subject and his/her parent(s) or guardian(s), when applicable, of all pertinent aspects of the trial and the subject's consent or the subject's assent and his/her parent(s)/legal guardian's written informed consent will be obtained. An initial physical assessment will be performed and relevant medical history will be obtained. If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

After providing a blood sample, and according to the randomization list, subjects will receive the study vaccines (Group I) or study vaccine + saline placebo (Groups II and III)

by an unblinded study vaccine administrator. The subjects and their parents/legal guardians, where applicable, will be blinded to the study vaccine given. Both vaccines and saline placebo will be administered intramuscularly (IM) in the deltoid muscle: in Group I Men ACWY vaccine will be administered in the right arm and Tdap vaccine in the left arm, in Groups II and III, study vaccine (Tdap or Men ACWY) will be administered into the left arm and saline placebo in the right arm. The subjects will remain in the clinic for 30 minutes following immunization to assess for any immediate reactions. During Visit 1, subjects and subjects' parents/legal guardians, where applicable, will be instructed on how to take the axillary temperature. In addition, the subjects and the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a Diary Card for the study Days 1-29 to record local and systemic reactions, body temperature, all Adverse Events and medications taken as describe in Table 1. The diary cards will be collected during the following site visit.

At study Days 3 (+3) and 8 (+3) the investigator or designee will contact the subjects and/or their parents/legal guardians, if necessary, to determine the subjects' health status and to remind the subjects and/or subjects parents/legal guardians to record local and systemic reactions, adverse events and concomitant medications on the Diary Cards. The subjects and/or subjects' parents/legal guardians will be asked to report any medical problems that are of concern to them to the investigator or designee at this time. The information obtained during the telephone contact will be recorded on the Telephone log.

At Visit 2 (Study Day 29, window 29-44 days after vaccination), subjects will return the Diary Cards to the clinic and will provide the 2nd blood draw. During the visit, the investigator (or delegated study physician) will review the Diary card and the Telephone log in the presence of the subject, to validate the information recorded on them. After the reconciliation, the information obtained will be recorded on the appropriate subject's case report form (CRF). The subjects and/or the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a worksheet for the study Days 30-181 to record AEs, medically significant AEs and medications taken as detailed in Table 1.

At study Day 181 (±15 days), subjects and/or their parents/legal guardians, where applicable, will be contacted to assess the health status of the subject and to discuss about safety information reported into the worksheet. Subjects and/or their parents/legal guardians will be asked to return the worksheet to the clinic by mail using a pre-printed envelope. Information from the worksheet will be reported into subject's CRF.

Subjects belonging to Group II and III will be respectively offered one single dose of licensed Men C or Td (or Tdap) vaccine, to be administered outside study evaluation and procedures.

Table 1 summarizes relevant medical history and safety assessments:

Table 1

Medical History: any significant past diagnoses including allergies, hospitalizations, major surgeries requiring in-patient hospitalization, any conditions requiring	From birth

prescription or chronic medication or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	
Vaccination History	From birth
Immediate reactions: signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 minutes after vaccination
Temperature: axillary temperature	For 7 days (Day 1 – 7)
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
Systemic reactions: chills, nausea, malaise, myalgia, arthralgia, and headache *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
All Adverse Events	For 7 days (Day 1 – 7)
Adverse Events: AEs necessitating a physician's visit and/or leading to Emergency Room visit and/or resulting in premature withdrawal from the study.	From Day 8 to Day 29
Medically significant AE: AE requiring a physician visit and/or leading to Emergency Room visit (pre-planned visits, medical office visits for routine medical care and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, and contact dermatitis will not be collected) and/or resulting in subject's withdrawal from the study.	From Day 30 to Day 181
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified. If an SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis (formerly Chiron) Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 181
Medications: All prescription medications and vaccinations	90 days before Visit 1
All prescription and non-prescription medications (with the exception of minerals, supplements and vitamins)	For 7 days (Day 1 – 7)
Any prescription and non-prescription medications (with the exception of minerals, supplements and vitamins) used to treat any SAE and other AE	From Day 8 to Day 29
Any prescription medication for treatment of SAE, medically significant AE requiring a physician visit or leading to Emergency Room visit	From Day 30 to Day 181

NUMBER OF SUBJECTS PLANNED:

Approximately 1000 healthy subjects 11-25 years of age will be enrolled and randomized in a 1:1:1 ratio to receive:

Group I (333 subjects): Tdap vaccine + Novartis (formerly Chiron) Men ACWY vaccine

Group II (333 subjects): Tdap vaccine + saline placebo

Group III (333 subjects): Novartis (formerly Chiron) Men ACWY + saline placebo

A total of 900 evaluable subject (300 for each vaccination group) are necessary. Considering possible drop outs, the sample size has been increased by a suitable percentage

SUBJECTS CHARACTERISTICS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Healthy subjects 11-25 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are male and female:

1. 11-17 years of age inclusive who have given their written assent and whose parents or legal guardians have given written informed consent at the time of enrollment; OR 18-25 years of age, mentally competent, and able to give the written informed consent prior to study entry
2. available for all visits and telephone calls scheduled for the study
3. in good health as determined by:
    - medical history
    - physical assessment
    - clinical judgment of the investigator
4. who have received the primary immunization with a vaccine containing DT or DTaP antigens and a T, Td or Tdap booster dose at least 5 years prior to study entry.

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling to give their written assent (subjects aged 11-17 years), when applicable
2. who (subjects aged 18-25 years) or whose parents or legal guardians (for subjects aged 11-17 years) are unwilling or unable to give written informed consent to participate in the study;
3. who and/or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;
4. who had a previous ascertained or suspected disease caused by *N. meningitidis*;
5. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* infection within 60 days prior to enrollment;

6. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of OMP-containing Hib vaccines is permitted);
7. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;
8. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within study period (Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination);
9. who have received a live viral vaccine within 60 days prior to enrollment;
10. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (e.g., axillary temperature ≥38°C) within 3 days prior to enrollment;
11. who have any serious acute, chronic or progressive disease (e.g., any history of neoplasm, cancer, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment);
12. who have epilepsy or any progressive neurological disease;
13. who have a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
14. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
    - receipt of immunostimulants
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study
15. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
16. who have Down's syndrome or other known cytogenic disorders;
17. who are pregnant or unwilling to do a pregnancy test or attest to not being pregnant;

18. who are not taking or unwilling to take sufficient measures to avoid pregnancy occurring for the duration of the study period. If sexually active, the subject must have been using one of the accepted birth control methods at least two months prior to study entry;
19. who and/or whose families are planning to leave the area of the study site before the end of the study period;
20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Assay). It is therefore strongly recommended to postpone a blood draw of 14 days if the subject has received oral or parenteral antibiotic in a one-a-day treatment and of 7 days in case of twice-a-day treatment.

TEST VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Men ACWY conjugate vaccine

The investigational Novartis (formerly Chiron) Meningococcal ACWY conjugate (Men ACWY) vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the liquid Men CWY component. After reconstitution the Men ACWY vaccine will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

One 0.5 mL dose of the Novartis (formerly Chiron) Men ACWY vaccine will be administered by IM injection in the deltoid area.

Tdap vaccine (GSK Boostrix®)

Composition	Quantity per 0.5 mL dose

Diphtheria Toxoid	2.5 Lf
Tetanus Toxoid	5 Lf
Pertactin	2.5 mcg
FHA	8 mcg
Inactivated PT	8 mcg
Sodium chloride	(b) (4) mg
Tween 80	=<100 mcg
Formaldehyde	=<100 mcg
Al(OH)3	(b) (4) mg
(b) (4)	(b) (4)
WFI	Qs to 0.5 mL

One 0.5 mL dose of Boostrix® vaccine will be administered IM in the deltoid area.

NOTE: Because study vaccines have different appearance in the syringe, vaccinations and safety assessments will be each performed by different study personnel to ensure blinding.

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Saline Placebo

Composition	Quantity per 0.5 mL dose
Sodium chloride	4.5 mg
WFI	Qs to 0.5 mL

One 0.5 mL dose of saline placebo will be administered IM in the deltoid area

CONCOMITANT VACCINES:

No concomitant vaccines will be administered for the whole duration of the study.

Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination. This vaccination will be reported as concomitant medications into subject's CRF.

MEASURES OF IMMUNOGENICITY:

Primary:

- the percentage of subjects with antibody levels against diphtheria toxin ≥ 1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the percentage of subjects with antibody levels against tetanus toxin ≥ 1 IU/mL at 1 month after immunization, as measured by ELISA assay
- seroresponse (4-fold increase as measured by ELISA) to Tdap for pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (PRN)

Secondary

- the percentage of subjects with antibody levels against diphtheria toxin ≥ 0.1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the percentage of subjects with antibody levels against tetanus toxin ≥ 0.1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the anti-diphtheria and anti-tetanus geometric mean concentration (GMC) at baseline and at one month after vaccination, and GMC increase (geometric mean ratio, GMR) from baseline
- the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroup A, C, W and Y, at 1 month after vaccination
- Seroresponse to Novartis MenACWY is defined as an hSBA titer ≥ 1:8 if the subject has an hSBA titer < 1:4 at baseline. If the subject has an hSBA titer ≥ 1:4 at baseline, then seroresponse is defined as the subject achieving a titer post injection of at least four times the subject's baseline hSBA titer (4-fold increase?).
- the percentage of subjects with hSBA titer ≥ 1:4 and hSBA titer ≥ 1:8 against *N. meningitidis* serogroups A, C, W and Y, at 1 month after vaccination
- hSBA geometric mean titer (GMT) against *N. meningitidis* serogroups A, C, W and Y at baseline and at one month after vaccination, and hSBA GMT increase (GMR) from baseline

The ability of Novartis MenACWY vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Assay, hSBA) will be measured in a subset of 150 randomly selected subjects for groups I and III.

MEASURES OF SAFETY:

The measures of safety to be used in this study consist of local and systemic reactions, axillary temperature, and other AEs. See Table 1.

SEROLOGY:

Both the ELISA and the hSBA analyses will be performed at:

Novartis (formerly Chiron) Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone: +49 (0)6421 39 3439/3712

Other laboratories may be employed, as directed by the sponsor.

In particular the Pertussis ELISA test may be performed at:
(b) (4)

CRITERIA FOR ASSESSING IMMUNOGENICITY OBJECTIVES:

The immunogenicity of the Tdap when given concomitantly with MenACWY (Group I) will be considered non-inferior to that of Tdap when given alone (Group II), if for all five antigens the lower limit of the two-sided 95% confidence interval (CI) for the (Tdap + MenACWY *minus* Tdap) difference in the response percentage will be greater than -10%. (i.e., Tdap + MenACWY *minus* Tdap > -10%).

CRITERIA FOR ASSESSING SAFETY OBJECTIVES:

Number of subjects with reported local and systemic reactions as well as number of subjects with reported serious adverse events and/or all adverse events up to day 7 and/or medically significant adverse events, will be calculated per vaccination group.

STATISTICAL HYPOTHESIS:

Primary

The null hypothesis associated with the primary immunogenicity objective is that for at least one antigen the underlying percent response in group I is at least 10% lower than in Group II (i.e., Tdap + MenACWY *minus* Tdap ≤ -10%)

Secondary

The first secondary immunogenicity objective is to precisely estimate the percentage of subjects with hSBA seroresponse, as defined above, at one month after the vaccination with MenACWY in study vaccine group I and III

STATISTICAL POWER CONSIDERATIONS:
Primary

The table below shows, for various underlying response percentages, the power to reject the null hypothesis for each antigen with a one-sided significance level (α) of 0.025. Assuming the results for the five antigens are independent, to have at least 80% power for non-inferiority for all five antigens, a power of at least 95.6% for each antigen is needed. (b) (4) version (b) (4) was used to perform the calculations.

Percent of responders Group I Tdap + MenACWY	Percent of responders Group II Tdap	Power to demonstrate non-inferiority for any antigen (N per group = 333 and 1-sided $\alpha = 0.025$)
70%	70%	80%
75%	75%	84%
80%	80%	89%
85%	85%	95%
90%	90%	>99%
95%	95%	>99%

Secondary

The precision afforded with a sample size of 150 evaluable subjects receiving MenACWY vaccine given concomitantly with Tdap or alone (Group I and III) - as measured by the two-sided 95% confidence interval (CI) - depends on the observed percentage of seroresponse as follow:

Observed hSBA seroresponse	**95% CI**
75%	67% - 82%
78%	71% - 84%
80%	73% - 86%
82%	75% - 88%
85%	78% - 90%
88%	82% - 93%
90%	84% - 94%
92%	86% - 96%
95%	90% - 98%
98%	94% - 100%
99%	98% - 100%

INTERIM ANALYSIS:

After all subjects have completed Visit 2, a group-unblinded preliminary analysis may be performed to assess immunogenicity.

In addition, an overall preliminary analysis may be performed to assess safety, when all subjects have completed the 7-day follow-up after vaccination (local and systemic reactions and body temperature within 7 days of immunization and SAEs).

The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Novartis (formerly Chiron) BCDM standard operating procedure entitled “Interim Analysis in a Clinical Trial.”

TIME AND EVENTS TABLE:

Study Day (window)	Day 1	Day 3 (+3) ☎	Day 8 (+3) ☎	Day 29 (+15)	Day 181 (±15) ☎
Visit Number Procedures	**1**			**2**	
Obtain Informed Assent and Consent	X				
Medical History	X				
Physical Assessment	X			X	
Obtain Blood Sample	X			X	
Administer Study Vaccine(s) and/or placebo	X				
Injection-site Examination	X			X	
Assess Local and Systemic Reactions; all Adverse Events* and Axillary Temperature	X	X	X		
Prior and Concomitant Medications	X	X	X	X	X
Adverse Events*			X	X	
Medically Significant Adverse Events*				X	X
Serious Adverse Events	X	X	X	X	X
Study Termination					X

Note: Day 1 is defined as the day of study vaccination.

*Please refer to Table 1

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
AP	Analysis Plan
BCDM	Biostatistics and Clinical Data Management
CDC	Center for Disease Control and Prevention
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRF	case report form
CRM	Cross Reacting Material
CRO	Clinical Research Organization
D	Diphtheria
DCF	Data Clarification Form
DT	Diphtheria Tetanus
DTaP	Diphtheria Tetanus acellular Pertussis
EC	ethics committee
ELISA	Enzyme Linked Immunosorbent Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentrations
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GSK	Glaxo Smith Kline
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
hSBA	human Serum Bactericidal Assay
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IM	Intramuscular(ly)
IRB	Institutional Review Board
ITT	intention-to-treat
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MenA	Meningococcal A
MenACWY	Meningococcal ACWY
MenC	Meningococcal C
MenCWY	Meningococcal CWY
MITT	modified intention-to-treat
OMP	Outer Membrane Protein

PP	per protocol
PT	Pertussis Toxin
SAE	serious adverse event
SOP	standard operating procedure
T	Tetanus
Td	Tetanus diphtheria
Tdap	Tetanus diphtheria acellular pertussis
US	United States
WHO	World Health Organization
WMA	World Medical Association

Definitions of Terms

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

End of Trial: The End of Trial corresponds to the last visit/telephone contact of the last subject undergoing the trial.

Local and Systemic Reactions: Selected local and systemic AEs are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within 7 days after immunization are herein termed "local and systemic reactions."

Month, Day: Study months are based upon 28-day cycles. The study day refers to the number of days after enrollment, with the day of first vaccination being designated day 1.

Serious Adverse Event: Any experience or reaction that suggests a significant hazard, contraindication, side effect, or precaution. These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital abnormality, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate medical judgment, may jeopardize the subject. Vaccine failure should also be considered as a serious adverse event (SAE).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Study Monitor: Study Monitor and CRA are used synonymously.

2. ETHICS

2.1 Approval of Study Protocol

Novartis (formerly Chiron) or the investigator will provide the ethics committee (EC) or institutional review board (IRB) with all appropriate material, including the informed consent document, according to the local regulation. The EC or IRB should also be asked for a written statement regarding the composition of the committee and should comply with GCP and with the applicable regulatory requirement(s). The trial will not be initiated until appropriate EC or IRB approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. Prior to enrollment, the sponsor and the investigator must exchange written confirmation that their ethical and legal responsibilities have been observed. The EC or IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. Appropriate reports on the progress of the study will be made to the EC or IRB and the sponsor by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the sponsor.

2.2 Ethical Conduct and Good Clinical Practice

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000 and the Note of Clarification of Paragraph 29 added by the WMA General Assembly, Washington 2002) Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). Specifically, this trial is based on adequately performed laboratory and animal experimentation; the trial will be conducted under a protocol reviewed and approved by an EC or IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed. A copy of the ICH GCP guidelines and of the Declaration of Helsinki will be included in the investigator's study file.

2.3 Informed Consent of Subject and Confidentiality

2.3.1 Informed Consent of Subject

The investigator is responsible to obtain informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form to the legally acceptable representative. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights the information should comprise that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject and/or the subject's legally acceptable representative should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and/or by the subject's legally acceptable representative and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

In addition, the subject should be informed about the trial according to its capacity of understanding. Oral and written information is provided. In case of minors the information should be given by staff with experience with minors. If possible, the subject should sign and personally date a written informed consent as affirmatively agreement to participate in the clinical trial. Depending on the subject's capability of assessing the given information and forming an opinion the subject's explicit wish to refuse participation must be respected, even if consent is given by the legally acceptable representative. This applies also to the wish to withdraw from the trial.

If the subject or his/her legally acceptable representative is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject or his/her legally acceptable representative has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject's rights were accurately explained to, and apparently understood by the subject or the legally acceptable representative and that informed consent was given freely.

The investigator will provide a copy of the signed informed consent documents to the subject or to the subject's legally acceptable representative, and will maintain the original(s) in the investigator's study file.

The written informed consent form and any other written information should be revised whenever important new information becomes available that may be relevant to the legally acceptable representative's and subject's consent. Any revised written informed consent form, and written information should receive EC's or IRB's approval before use.

The subject and/or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

2.3.2 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor. Study findings stored on a computer will be subject to local data protection laws. The subject, or where applicable, the subject's legally acceptable representative(s) will be informed that representatives of the sponsor, EC or IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

The investigator or designee will maintain a personal list of subject numbers and subject identification codes to enable records to be found at a later date.

2.4 Liability and Insurance

The involved parties will be insured, in accordance with applicable laws and regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. The sponsor will provide adequate insurance for the investigator according to regulatory requirement(s). If required by local law, study subjects enrolled into this clinical trial will also be insured against any injury resulting from the clinical study.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to trial initiation, the investigator at the site must provide to Novartis (formerly Chiron) a fully executed and signed financial disclosure form.

The trial will be administered and monitored by employees or representatives of Novartis (formerly Chiron) Vaccines. Study Monitors will monitor the site on a periodic basis and perform verification of source documentation for each subject. The Medical Monitor will be readily available to provide appropriate medical expertise on trial related medical questions. Novartis (formerly Chiron) Regulatory Affairs or Pharmacovigilance Department will be responsible for the timely reporting of serious adverse events (SAEs).

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Contract Research Organization	(b) (4)

4. INTRODUCTION

Meningococcal disease is caused by a gram-negative diplococcus, *Neisseria meningitidis*.[1] Invasive infection by *N. meningitidis* usually results in bacteremia and/or meningitis, and can be complicated by purpuric rash (meningococcemia), arthritis, myocarditis, pericarditis, endophthalmitis, or pneumonia. This disease often cannot be distinguished clinically from other forms of acute bacterial meningitis and sepsis caused by *Haemophilus influenzae* or *Streptococcus pneumoniae*. The signs of meningococcal meningitis include headache, stiff neck, fever, chills, malaise, and prostration. Asymptomatic colonization of the upper respiratory tract by encapsulated *N. meningitidis* is common. Transmission is thought to be via droplets of respiratory tract secretions.[2] Only a small percentage of colonized persons develop disease.

The case-fatality rate for meningococcal disease ranges from 2% to 40%, being highest in patients with meningococcemia and lowest in patients with mild forms of bacteremia or uncomplicated meningitis.[3 – 10] In the more severe cases, fatalities may be a result of cerebral damage or endotoxic shock.

The overall incidence of meningococcal disease in the United States (US) during recent decades has been ~0.9 to 1.5 cases per 100,000 population, but epidemic rates in sub-Saharan African, mainly due to meningococcal serogroup A, have been more dramatic (~500-1000 cases per 100,000).[11] While known risk factors, such as overcrowded housing conditions, may contribute to differences in attack rates, these difference in disease incidence are not entirely well understood.[12 – 14]

The incidence of meningococcal disease is also influenced by the maturation of the human immune response and the variable susceptibility of individuals at different ages.[15] Neonates are relatively protected against developing meningococcal disease as a result of passive acquisition of transplacental maternal antibodies.[16] With increasing age, there is a decreasing level of maternal antibodies and the infant becomes more susceptible to developing meningococcal disease. The lowest antibody levels are found in infants between 6 months and 2 years of age; natural immunity begins to be acquired after 2 years of age. Meningococcal disease is, therefore, predominantly a disease of infants and young children, although increased disease incidence can also occur in adolescents and adults. Examples of the latter include epidemics among military recruits during basic training and increased meningococcal disease rates among college students residing in dormitories.[11, 16 – 18]

N. meningitidis causes life threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified, with serogroups A, B, C, W135 and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all 5 of the most common serogroups responsible for invasive disease.

Licensed tetravalent polysaccharide vaccines against serogroup A, C, W135 and Y have been available for many years and are widely used. However they do not provide long-term protection and are poorly immunogenic, even in the short-term, in children below 2 years of age.[19 – 24]

The immunogenicity of polysaccharides can be improved by chemical conjugation to a protein carrier in order to elicit a T-cell dependent antibody response. Therefore, new combined conjugate vaccines containing capsular oligosaccharides conjugated to a protein carrier have been developed, and successfully licensed, to prevent disease caused by *H. influenzae* type b, *Streptococcus pneumoniae,* and *N. meningitidis*.[25 – 29] In contrast to plain polysaccharide vaccines, the polysaccharide-protein conjugate vaccines induce T-cell dependent immune responses, are immunogenic in young infants, and induce long-term protection.

Based upon the recent, successful development of conjugate vaccines, Novartis (formerly Chiron) is developing a Meningococcal ACWY (Men ACWY) Conjugate Vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM197 (a non-toxic mutant of diphtheria toxin).

An FDA panel recently recommended approval of Tdap booster targeting >11 years old. US based analysis for use in adolescents projected that vaccination of people aged 10-19 during a 10-year period would prevent up to 1.8 million cases of pertussis. According to the CDC, there were almost 20,000 cases of pertussis in 2004 – the highest number of reported cases in more than 40 years. In addition, 39% of cases reported to the CDC in 2003 occurred in adolescents 10-19 years of age. Adolescents, in whom classic signs and symptoms of pertussis are often absent, may go undiagnosed and be the source of infection for susceptible infants and other family members.

The main objective of the proposed phase 3 study is to describe and compare the immunogenicity profile of a single dose of Novartis (formerly Chiron) Men ACWY administered alone or concomitantly with a licensed combined Tdap vaccine (Boostrix®, GSK), with that of a single dose of Tdap, when administered to healthy subjects 11-25 years of age.

Novartis (formerly Chiron) Men ACWY conjugate vaccine has already been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 1300 subjects (from infants up to 17 years old) have received at least one dose of the formulation of Novartis (formerly Chiron) Men ACWY conjugate vaccine being tested in this study.

A comprehensive review of investigational Novartis (formerly Chiron) Men ACWY conjugate vaccine is contained in the Investigator's Brochure or Summary of Product Characteristics supplied by Novartis (formerly Chiron) Vaccines; this document should be reviewed prior to initiating the study.

5. STUDY OBJECTIVES

5.1 Immunogenicity Objectives

Primary

To demonstrate that the immunogenicity of a single dose of Tdap vaccine, separately but concomitantly administered with Novartis (formerly Chiron) MenACWY, is not inferior to that of a single dose of Tdap vaccine, concomitantly administered with a saline placebo.

Secondary

- To compare the immunogenicity of a single dose of Tdap vaccine when given separately but concomitantly administered with Novartis MenACWY, to that of a single dose of Tdap vaccine, concomitantly administered with a saline placebo. Immunogenicity response of Tdap is defined as: 1) percentage of subjects with ELISA anti-diphtheria toxin ≥ 0.1 IU/mL and anti-tetanus toxin ≥ 0.1 IU/mL at one month after vaccination; 2) anti-diphtheria, anti-tetanus, anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), and anti-pertactin (anti-PRN) ELISA geometric mean concentration (GMC) at baseline and at one month after vaccination, and GMC increase (geometric mean ratio, GMR) from baseline at one month after vaccination.

- To evaluate the immunogenicity of a single dose of Novartis MenACWY vaccine, separately but concomitantly administered with Tdap, and that of a single dose of Novartis MenACWY vaccine, concomitantly administered with a saline placebo. Immunogenicity response of Novartis MenACWY is defined as: 1) percentage of subjects with hSBA seroresponse; 2) percentage of subjects with hSBA ≥ 1:4 and percentage of subjects with hSBA ≥ 1:8 at one month after vaccination; 3) hSBA geometric mean titer (GMT) at baseline and at one month after vaccination, and GMT increase (GMR) from baseline at one month after vaccination.

5.2 Safety Objectives

To describe and compare the safety profile following a single dose of Novartis (formerly Chiron) Men ACWY + Tdap vaccines to that of either Tdap + saline placebo or Novartis (formerly Chiron) Men ACWY + saline placebo when administered to healthy subjects 11-25 years of age, defined as percentage and number of subjects with:

- Immediate hypersensitivity reactions following vaccination
- Local and systemic reactions and axillary temperature reported during the period Day 1 - Day 7 after vaccination
- Adverse events (AEs) reported during the period Day 1 - Day 29 after vaccination

- Medically significant AEs reported during the period Day 30 - Day 181 after vaccination
- Serious adverse events (SAEs) reported for the whole duration of the study

6. OVERALL STUDY DESIGN

6.1 Overall Study Design and Plan – Description

6.1.1 Overall Study Design

This a phase 3, observer-blind, multi-center, randomized, controlled study in healthy subjects aged 11-25 years.

The main objective of the study is to describe and compare the immunogenicity profile of a single dose of Novartis (formerly Chiron) Men ACWY administered alone or concomitantly with a licensed combined Tdap vaccine (Boostrix®, GSK), with that of a single dose of Tdap.

Subjects will be included in the study if in good health as judged by physical examination and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 1000 healthy subjects aged 11-25 years will be randomized in a 1:1:1 ratio to receive either concomitant administrations of Tdap + Novartis (formerly Chiron) Men ACWY vaccines (Group I), or Tdap vaccine + saline placebo (Group II), or Novartis (formerly Chiron) Men ACWY + saline placebo (Group III).

Group (N)	**Day 1 Visit 1**	**Day 29 Visit 2**
I (333)	Serology Tdap + Men ACWY	Serology
II (333)	Serology Tdap + saline	Serology
III (333)	Serology Men ACWY + saline	Serology

At the enrollment visit (Visit 1), the investigator, or a person designated by the investigator, should fully inform the subject and his/her parent(s) or guardian(s), when applicable, of all pertinent aspects of the trial and the subject's consent or the subject's assent and his/her parent(s)/legal guardian's written informed consent will be obtained. An initial physical assessment will be performed and relevant medical history will be obtained. If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

During the same visit (Visit 1, Day 1), prior to administration of study vaccine, a blood sample (10 mL) will be obtained for serologic evaluation. After providing a blood sample, and according to the randomization list, subjects will receive the study vaccines (Group I) or study vaccine + saline placebo (Groups II and III) by an unblinded study vaccine administrator. The subjects and their parents/legal guardians, where applicable, will be blinded to the study vaccine given. Both vaccines and saline placebo will be administered intramuscularly (IM) in the deltoid muscle: in Group I Men ACWY vaccine will be administered in the right arm and Tdap vaccine in the left arm, in Groups II and III, study vaccine (Tdap or Men ACWY) will be administered into the left arm and saline placebo in the right arm. The subjects will remain in the clinic for 30 minutes following immunization to assess for any immediate reactions. During the visit subjects and subjects' parents/legal guardians, where applicable, will be instructed on how to take the axillary temperature. In addition, the subjects and the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a Diary Card for the study Days 1-29 to record local and systemic reactions, body temperature, all Adverse Events and medications taken as describe in Table 1. The diary cards will be collected during the following site visit.

At study Days 3 (+3) and 8 (+3) the investigator or designee will contact the subjects and/or their parents/legal guardians, if necessary, to determine the subjects' health status and to remind the subjects and/or subjects' parents/legal guardians guardians to record local and systemic reactions, adverse events and concomitant medications on the Diary Cards. The subjects and/or subjects' parents/legal guardians will be asked to report any medical problems that are of concern to them to the investigator or designee at this time. The information obtained during the telephone contact will be recorded on the Telephone log.

At Visit 2 (Study Day 29, window 29-44 days after vaccination), subjects will return the Diary Cards to the clinic, and post vaccination blood draw (10 mL) will be collected. During the visit, the investigator (or delegated study physician) will review the Diary card and the Telephone log in the presence of the subject, to validate the information recorded on them. After the reconciliation, the information obtained will be recorded on the appropriate subject's case report form (CRF). The subjects and/or the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a worksheet for the study Days 30-181 to record AEs, medically significant AEs and medications taken as detailed in Table 1.

At study Day 181 (±15 days), subjects and their parents/legal guardians, where applicable, will be contacted to assess the health status of the subjects and to discuss about safety information reported into the worksheet. Subjects and/or their parents/legal guardians will be asked to return the worksheet to the clinic by mail using a pre-printed envelope. Information from the worksheet will be reported into subject's CRF.

Subjects belonging to Group II and III will be respectively offered one single dose of licensed MenC or Td (or Tdap) vaccine, to be administered outside study evaluation and procedures.

Table 1 summarizes relevant medical history and safety assessments:

Table 1

Medical History: any significant past diagnoses including allergies, hospitalizations, major surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	From birth
Vaccination History	From birth
Immediate reactions: signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 minutes after vaccination
Temperature: axillary temperature	For 7 days (Day 1 – 7)
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
Systemic reactions: chills, nausea, malaise, myalgia, arthralgia, and headache *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
All Adverse Events	For 7 days (Day 1 – 7)
Adverse Events: AEs necessitating a physician's visit and/or leading to Emergency Room visit and/or resulting in premature withdrawal from the study.	From Day 8 to Day 29
Medically significant AE: AE requiring a physician visit and/or leading to Emergency Room visit (pre-planned visits, medical office visits for routine medical care and common acute conditions, such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, and contact dermatitis will not be collected) and/or resulting in subject's withdrawal from the study.	From Day 30 to Day 181
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified. If an SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis (formerly Chiron) Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 181
Medications: All prescription medications and vaccinations	90 days before Visit 1
All prescription and non-prescription medications (with the exception of minerals, supplements and vitamins)	For 7 days (Day 1 – 7)

Any prescription and non-prescription medications (with the exception of minerals, supplements and vitamins) used to treat any SAE and other AE	From Day 8 to Day 29
Any prescription medication for treatment of SAE, medically significant AE requiring a physician visit or leading to Emergency Room visit	From Day 30 to Day 181

Please also refer to the study Flow Chart (section 6.5.4).

6.1.2 Planned Duration of Study

Expected subject enrollment interval: 6 months

Duration of individual subject's participation: 6 months

Total duration of study: 12 months

End of Trial: corresponds to the last visit/telephone contact of the last subject undergoing the trial (LSLV).

6.1.3 Premature Discontinuation of the Study

The sponsor, or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study medication/vaccines etc.) will be returned to the sponsor.

6.1.3.1 Stopping/Pausing Rules

There are no predetermined stopping rules other than those described in section 6.1.3.

6.2 Discussion of Overall Study Design

This phase 3 study utilizes several standard features of clinical study design intended to reduce bias, including the random assignment of subjects to treatment groups, the use of a placebo and an observer-blind design. Because study vaccines have different appearance in the syringe, vaccinations and safety assessments will be each performed by different study personnel to ensure blinding. The subjects, their parents/legal guardians and the investigators will be blinded to the study vaccine given.

The design features were selected because of their well-recognized acceptance as scientifically appropriate.

This clinical trial, due to the involvement of minors, has been designed to minimize pain, discomfort, fear and any other foreseeable risks

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Individuals eligible for enrollment in this study are male and female:

1. 11-17 years of age inclusive who have given their written assent and whose parents or legal guardians have given written informed consent at the time of enrollment; OR 18-25 years of age, mentally competent, and able to give the written informed consent prior to study entry;

2. available for all visits and telephone calls scheduled for the study;

3. in good health as determined by:

    - medical history
    - physical assessment
    - clinical judgment of the investigator

4. who have received the primary immunization with a vaccine containing DT or DTaP antigens and a T, Td or Tdap booster dose at least 5 years prior to study entry.

Informed consent must be obtained for all the subjects before enrollment into the study.

6.3.2 Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling to give their written assent (subjects aged 11-17 years), when applicable

2. who (subjects aged 18-25 years) or whose parents or legal guardians (for subjects aged 11-17 years) are unwilling or unable to give written informed consent to participate in the study;

3. who and/or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;

4. who had a previous ascertained or suspected disease caused by *N. meningitidis*;

5. who had household contact with and/or intimate exposure to an individual with culture-proven *N meningitidis* infection within 60 days prior to enrollment;

6. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of OMP-containing Hib vaccines is permitted);

7. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;

8. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within study period (Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination);

9. who have received a live viral vaccine within 60 days prior to enrollment;

10. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (e.g., axillary temperature ≥ 38°C) within 3 days prior to enrollment;

11. who have any serious acute, chronic or progressive disease (e.g., any history of neoplasm, cancer, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition). (Exception: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment);

12. who have epilepsy or any progressive neurological disease;

13. who have a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;

14. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):

    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)

    - receipt of immunostimulants

- receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study

15. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

16. who have Down's syndrome or other known cytogenic disorders;

17. who are pregnant or unwilling to do a pregnancy test or attest to not being pregnant;

18. who are not taking or unwilling to take sufficient measures to avoid pregnancy occurring for the duration of the study period. If sexually active, the subject must have been using one of the accepted birth control methods at least two months prior to study entry;

19. who and/or whose families are planning to leave the area of the study site before the end of the study period;

20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Assay). It is therefore strongly recommended to postpone a blood draw of 14 days if the subject has received oral or parenteral antibiotic in a one-a-day treatment and of 7 days in case of twice-a-day treatment.

6.3.3 Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

The subject will be clinically monitored after withdrawal, the cause of which will be recorded in detail on the "Study Termination" CRF and "Adverse Events" and/or "Prior and Concomitant Medications/Blood Products" CRF and, where appropriate, on the subject's medical records. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section 6.5.4.5.

Whenever possible, the tests and evaluations listed for the termination visit will be carried out.

Withdrawn subjects will not be replaced.

6.4 Vaccines

6.4.1 Vaccines Administered

Subjects will be randomly assigned in a 1:1:1 ratio, to one of the following vaccination groups:

Group I: separate but concomitant administration of 1 dose of Tdap vaccine (GSK Boostrix®) and 1 dose of Novartis (formerly Chiron) Men ACWY vaccine

Group II: separate but concomitant administration of 1 dose of Tdap vaccine (GSK Boostrix®) and 1 dose of placebo

Group III: separate but concomitant administration of 1 dose of Novartis (formerly Chiron) Men ACWY vaccine and 1 dose of placebo

NOTE: Because study vaccines have different appearance in the syringe, vaccinations and safety assessments will be each performed by different study personnel to ensure blinding

6.4.2 Identity of Investigational Vaccine

6.4.2.1 Vaccine Composition

a) Investigational vaccine

Novartis (formerly Chiron) Men ACWY Conjugate Vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the liquid Men CWY component. One 0.5 mL dose of the Novartis (formerly Chiron) Men ACWY Conjugate Vaccine will be administered by IM injection in the deltoid area of the arm.

After reconstitution the Men ACWY Conjugate Vaccine will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)

Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

One 0.5 mL dose of the Novartis (formerly Chiron) Men ACWY vaccine will be administered by IM injection in the deltoid area.

Novartis (formerly Chiron) Men ACWY Conjugate Vaccine, lot nr. V79P39D1, expiry date 08/2007 will be used during the trial.

b) **Tdap vaccine (GSK Boostrix®)**

Licensed combined Tdap vaccine Boostrix® (manufactured by GSK Biologicals, Rixensart, Belgium) is supplied as a 0.5 mL dose.

Composition	Quantity per 0.5 mL dose
Diphtheria Toxoid	2.5 Lf
Tetanus Toxoid	5 Lf
Pertactin	2.5 mcg
FHA	8 mcg
Inactivated PT	8 mcg
Sodium chloride	(b) (4) mg
Tween 80	=<100 mcg
Formaldehyde	=<100 mcg
Al(OH)3	(b) (4) mg
(b) (4)	(b) (4)
WFI	Qs to 0.5 mL

One 0.5 mL dose of Boostrix® vaccine will be administered IM in the t deltoid area

c) **Saline Placebo**

Composition	Quantity per 0.5 mL dose
Sodium chloride	4.5 mg
WFI	Qs to 0.5 mL

One 0.5 mL dose of saline placebo will be administered IM in the t deltoid area

6.4.2.2 Vaccine Labeling, Storage and Packaging

All vaccine supplies must be stored between +2/+8 °C. Vaccines that have been stored differently from the sponsor's recommendations **must not** be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor.

The sponsor will supply the investigational vaccines and the saline placebo. The investigator (or pharmacist) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.

Novartis (formerly Chiron) Men ACWY Conjugate Vaccine

Novartis (formerly Chiron) Men ACWY Conjugate Vaccine will be supplied and packaged as a single dose per carton. One carton will contain two vials: one vial will contain the lyophilized powder of the Men A component and the second vial will contain the liquid solution of the Men CWY component.

For each study vaccine, the carton label contain the vaccine identifier and the following information:

Protocol Number:
Investigator's name:
Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at +2/+8°C
For Clinical Trial use only
Expiry date:
Lot number:
Site number:
Sponsor name:

The two vial labels will include the identity of the investigational product, a 5-digit blank to be completed with the subject number following randomization (put on the detachable label), the protocol number, the expiry date, the lot number, the required storage conditions, the sponsor's name and location, the cautionary statement "For clinical trial use only", and the directions for use.

Novartis (formerly Chiron) Men ACWY Conjugate vaccine is identified by a lot number. The last digit of the lot number is a letter that can differ within the same vaccine batch in case multiple packaging and/or labeling processes are performed. This has no impact on the vaccine composition or manufacturing process.

Tdap vaccine (GSK Boostrix®)

Boostrix® vaccine will be supplied and packaged as a single dose per carton. One carton will contain one pre-filled syringe containing a single dose of a fully liquid presentation of Tdap components.

An additional label including the a 5 digit blank to be completed with the subject number following randomization (put on the detachable label), the protocol number, the sponsors name and location, the cautionary statement "For Clinical trial use only" and the directions for use will be attached to the commercial carton box of the vaccine. The commercial vial labels for Boostrix® will remain intact.

Saline Placebo

Saline placebo will be supplied and packaged as a single dose per carton. One carton will contain one vial containing 2 mL of saline solution.

An additional label including the a 5 digit blank to be completed with the subject number following randomization (put on the detachable label), the protocol number, the sponsors name and location, the cautionary statement "For Clinical trial use only" and the directions for use will be attached to the commercial carton box of the saline solution.

The commercial labels will remain intact.

6.4.2.3 Vaccine Administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Directions for Reconstitution and Administration of Novartis (formerly Chiron) Men ACWY Conjugate Vaccine:

The lyophilized Novartis (formerly Chiron) Men A component requires preparation by reconstitution with the Novartis (formerly Chiron) Men CWY full liquid component:

- Gently agitate the Men CWY full liquid component vial;
- Draw up 0.6 mL of Men CWY into a suitable size syringe (i.e., 2 mL) and inject into the Men A lyophilized component vial to reconstitute;
- Gently shake the reconstituted vial until the Men A lyophilized powder is dissolved;

- Following reconstitution, the vaccine must be gently shaken and visually inspected before use. If any foreign particulate matter and/or variation of physical aspect are observed, DO NOT USE the vaccine and notify Novartis (formerly Chiron). DO NOT DISCARD the vaccine as it may be returned to Novartis (formerly Chiron) for inspection.

- If no particulate matter and/or variation of physical aspect are observed, using a new suitable gauge needle, withdraw 0.5 mL of reconstituted product, ensuring no air bubbles are present;

- Inject 0.5 mL of the reconstituted vaccine IM into the deltoid area of the arm

DO NOT inject intravascularly.

Directions for Administration of Boostrix and Placebo

- Visually inspect the appropriate vial before use. If any foreign particulate matter and/or variation of physical aspect are observed, DO NOT USE the vaccine and notify Novartis (formerly Chiron). DO NOT DISCARD the vaccine as it may be returned to Novartis (formerly Chiron) for inspection.

- If no particulate matter and/or variation of physical aspect are observed, using a new suitable gauge needle / syringe, inject 0.5 mL of product, ensuring no air bubbles are present, in the deltoid area.

DO NOT inject intravascularly.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Any axillary temperature ≥ 38°C or serious active infection is reason for delaying vaccination. Immunization should also be delayed according to instructions in section 6.3.3.

Standard immunization practices should be observed and care should be taken to administer the IM injections. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4.3 Method of Assigning Subjects to Vaccination Groups

Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 5-digit subject number. The first two digits identify the study site. The next three digits identify the subject within the site and will be assigned sequentially, with 001 corresponding to the first subject enrolled at any given site.

Subjects will be randomly assigned in a 1:1:1 ratio to one of the vaccination groups, following a randomization list.

6.4.4 Selection of Doses in the Study

The Novartis (formerly Chiron) Men ACWY Conjugate Vaccine dose used in this study is based upon data from preceding studies, which indicate that the 10-5-5-5µg formulation used in this study may provide enhanced immune response directed against the serogroup A component in comparison to other formulations.

6.4.5 Blinding

The trial is designed as an observer-blind study. During the study, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, except in an emergency. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. If the study vaccine code is supplied to the investigator in the event of an emergency, the study monitor must be notified immediately by the investigator. The date and time, along with the reason for the unblinding, should be noted. Study vaccine codes will not be freely available to the investigator or personnel monitoring the trial until after the completion of the trial and final data review

6.4.6 Prior and Concomitant Therapy

All prescription medication, including non-study vaccines, being taken by the subjects on entry to the study and all prescription medication given in addition to the study vaccine during this clinical trial are to be regarded as concomitant medication and must be documented on the “Prior and Concomitant Medications/Blood Products” CRF. All relevant medication (including vaccinations) prescribed to the subject within 90 days prior to the start of the study is to be recorded on the “Prior and Concomitant Medications/Blood Products” CRF.

No concomitant vaccines will be administered during Visit 1.

No other vaccines than those included in the protocol should be administered simultaneously with the study vaccine; if there is a medical need to administer other

vaccines, it is recommended to allow an interval of 30 days (60 days for live viral vaccines) after the administration of the study vaccine. *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and no less than 15 days after study vaccination)*

The following concomitant treatments are discouraged and, if used, might lead to a major protocol violation according to the medical judgment of the Novartis (formerly Chiron) physician (see exclusion criteria: Section 6.3.2) and withdrawal from the study:

- receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)

- receipt of immunostimulants

- receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study

- systemic antibiotic treatment taken in the 14 days prior to any blood draws, if the subject has received oral or parenteral antibiotic in a once-a-day treatment, or within the previous 7 days, in case of twice-a-day treatment.

Antipyretic medication should not be used for the prevention of fever before vaccinations. If a medication is given for the treatment of fever, the temperature should be taken again after 4 hours, to evaluate whether further treatment is necessary.

6.4.7 Vaccination Compliance

The unblinded personnel will be responsible for adequate and accurate accounting of vaccine usage. The investigator's unblinded designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be returned to the sponsor or destroyed at the investigational site according to the relevant Novartis (formerly Chiron) SOP. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.4.8 Adherence to Randomization List

An unblinded, appropriately qualified person, will prepare/administer the vaccine as indicated in the randomization list for the individual subject. The investigator as well as the Study Monitor will be blinded during the conduct of the study.

Adherence to randomization list will be verified by Novartis (formerly Chiron) Clinical Quality Assurance (CQA) by checking the randomization list against the vaccination records. A copy of the vaccine accountability log and administration log is to be sent to CQA, Novartis (formerly Chiron) Vaccines S.r.l., Via Fiorentina, 1, 53100 Siena, Italy, Fax +39 0577 278507, weekly during the enrollment period of this study

6.5 Immunogenicity and Safety Variables

6.5.1 Immunogenicity and Safety Measurements Assessed

The Time and Events Table in the Synopsis and section 6.5.5 describes the required evaluations.

6.5.2 Appropriateness of Measurements

The measures of immunogenicity used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic reactions routinely monitored in vaccine clinical trials as indicators of reactogenicity.

Immunogenicity of the study vaccines will be evaluated by the Novartis (formerly Chiron) Vaccines Clinical Serology laboratory (Klinische Serologie, Gebäude Z26, Emil-von-Behring Str. 76, 35041 Marburg, Germany) for the presence of bactericidal antibodies to *N. meningitidis* serogroups A, C, W_{135} and Y (b) (4) and for the presence of antibody levels against diphtheria, tetanus and pertussis.

Additional tests may be performed (e.g., ELISA for the presence of IgG antibodies to *N. meningitidis* serogroups A, C, W_{135}, Y capsular polysaccharide). Other laboratories may be employed, as directed by the sponsor.

In particular the Pertussis ELISA test may be performed at: (b) (4)
(b) (4)

6.5.3 Immunogenicity Variables

Primary:

- the percentage of subjects with antibody levels against diphtheria toxin ≥ 1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the percentage of subjects with antibody levels against tetanus toxin ≥ 1 IU/mL at 1 month after immunization, as measured by ELISA assay

- seroresponse (4-fold increase as measured by ELISA) to Tdap for pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (PRN)

Secondary

- the percentage of subjects with antibody levels against diphtheria toxin ≥ 0.1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the percentage of subjects with antibody levels against tetanus toxin ≥ 0.1 IU/mL at 1 month after immunization, as measured by ELISA assay
- the anti-diphtheria and anti-tetanus geometric mean concentration (GMC) at baseline and at one month after vaccination, and GMC increase (geometric mean ratio, GMR) from baseline
- the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroup A, C, W and Y, at 1 month after vaccination
- Seroresponse to Novartis MenACWY is defined as an hSBA titer ≥ 1:8 if the subject has an hSBA titer < 1:4 at baseline. If the subject has an hSBA titer ≥ 1:4 at baseline, then seroresponse is defined as the subject achieving a titer post injection of at least four times the subject's baseline hSBA titer (4-fold increase?).
- the percentage of subjects with hSBA titer ≥ 1:4 and hSBA titer ≥ 1:8 against *N. meningitidis* serogroups A, C, W and Y, at 1 month after vaccination
- hSBA geometric mean titer (GMT) against *N. meningitidis* serogroups A, C, W and Y at baseline and at one month after vaccination, and hSBA GMT increase (GMR) from baseline

The ability of Novartis MenACWY vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Assay, hSBA) will be measured in a subset of 150 randomly selected subjects for groups I and III.

6.5.4 Safety Variables

A brief medical history will be obtained and physical examination performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.1.1 and 6.5.5.

6.5.4.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can,

therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and Medical Monitor whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational vaccine has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

6.5.4.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Of note: a "possible vaccine failure" should be reported as a serious AE only if it resulted in an infectious disease which should have been prevented by the vaccine implied.

Adverse events which do not fall into these categories are defined as **non-serious**.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial. The types of procedures noted above should be prohibited during the trial whenever possible.

6.5.4.3 Local and Systemic Reactions

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post-vaccination, will be recorded on the "Local and Systemic Reactions" rather than the "Adverse Events" CRF.

Local Reactions:

Pain, erythema, induration

Systemic Reactions:

Chills, nausea, malaise, myalgia, arthralgia, and headache

Other indicators of Reactogenicity

Body temperature, use of analgesic/antipyretics, quality of life parameters (e.g., stayed home due to reaction)

6.5.4.4 Clinical Laboratory Tests

Not applicable

6.5.4.5 Documentation/Monitoring/Reporting of Safety Variables

All study subjects will be observed for at least 30 minutes after a vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena (such as rashes, itching, or other allergic manifestations). Each subject, or where applicable, the subject s' legally acceptable representative(s) will be instructed to complete a diary card for 29 days following vaccine(s) administration, to describe local reactions, systemic reactions and all adverse events (for 7 days after vaccination); AEs necessitating a physician's visit and/or leading to Emergency Room visit and/or resulting in premature withdrawal from the study (from Day 8 to Day 29). If a local and systemic reaction continues beyond 7 days after a vaccination, it will also be recorded on the "Adverse Events" CRF. If the subject recovers on the last day, then this fact will be recorded on the "Comments" CRF. All AEs must be reported and documented. The period of observation for adverse events extends from the time the subject gives informed consent until he or she undergoes the final study examination. This may include a period before and after an active treatment of an investigational product (study vaccine) or other medication.

All adverse events, regardless of severity, will be monitored by the investigator until resolution. All subjects experiencing adverse events - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory

explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an “Adverse Events” CRF and on the “Vaccine Serious Adverse Event” form, if necessary, which is part of the investigator’s study file. All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

In addition, any event resulting in a subject’s withdrawal from subsequent vaccinations or from follow-up should be reported according to the protocol instructions. All SAEs which occur during the course of the trial, whether considered to be associated with the study vaccination or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor: Francesca Ceddia, MD
Phone number: +39 0577 243831
Fax number: +39 0577 243551
E-mail: francesca.ceddia@novartis.com
Mobile phone: +39 328 7604990

Study Monitor: Laura Lauretti, PhD
Phone number: +39 0577 245219
Fax number: +39 0577 243551
E-mail: laura.lauretti@novartis.com

For trial related **emergencies out of office hours** please contact: +49 (0)151 12641663

As far as possible, all points raised on the “Vaccine Serious Adverse Event” form need to be addressed and faxed immediately to the Medical Monitor or Study Monitor. Afterwards the original form must be sent by post to the Medical Monitor/Study Monitor. The event must also be documented on the “Adverse Events” CRF. After receipt of the initial report, the Medical Monitor/Study Monitor will review the information and contact the investigator if it is necessary to obtain further information for assessment of the event. Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF(s) in addition to the outcome of the AE. Any serious or unexpected AE must be reported to the EC or IRB in a timely manner. Adequate documentation will be provided to the sponsor showing that the EC or IRB has been properly notified.

If required, a follow-up report including all new information obtained on the serious adverse event must be prepared and sent to the Medical Monitor *or* Study Monitor, or it will be collected by a representative of the sponsor. The report should be marked "Follow-up report".

The investigator will submit, on request, copies of all these reports to the EC or IRB and other relevant authorities.

Post-Study Events

Any AE occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine - and therefore a possible adverse drug reaction - must be reported.

6.5.5 Study Procedures and Flowchart

Informed consent must be obtained from the subject, or where applicable, the subject's legally acceptable representative(s) prior to the performance of any trial specific tests or evaluations, i.e., any unusual or non-routine procedures that involve risk, however trivial, to the subject.

TIME AND EVENTS TABLE:

Study Day (window)	Day 1	Day 3 (+3) ☎	Day 8 (+3) ☎	Day 29 (+15)	Day 181 (±15) ☎
Visit Number **Procedures**	**1**			**2**	
Obtain Informed Assent and Consent	X				
Medical History	X				
Physical Assessment	X			X	
Obtain Blood Sample	X			X	
Administer Study Vaccine(s) and/or placebo	X				
Injection-site Examination	X			X	
Assess Local and Systemic Reactions; all Adverse Events* and Axillary Temperature	X	X	X		
Prior and Concomitant Medications	X	X	X	X	X
Adverse Events*			X	X	
Medically Significant Adverse Events*				X	X
Serious Adverse Events	X	X	X	X	X
Study Termination					X

Note: Day 1 is defined as the day of study vaccination.

*Please refer to Table 1

Visit 1: Study Day 1

a. At Visit 1, the investigator, or a person designated by the investigator, should fully inform the subjects and subjects' parent(s)/guardian(s), when applicable, of all pertinent aspects of the trial and a written informed consent will be obtained. Subjects below 18 years of age will be asked to sign an assessment form based on the investigator's/parent's opinion about the ability of the subject to fulfill this task. A physical assessment to evaluate the subjects' health will be performed and relevant medical history and prior and concomitant medication information will be obtained. An assessment of inclusion and exclusion criteria will also be performed.

b. Privately review, with females of childbearing potential, their ability to become pregnant and commitment to practice appropriate birth control as determined by the investigator for the 180 days duration of the study. If sexually active, the subject must have been using one of the accepted birth control methods for at least two months prior to study entry. A urine pregnancy test will be performed on all female subjects of childbearing potential. Complete the Pregnancy test form as appropriate. (See exclusion criteria nr.17 and 18).

c. If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

d. Obtain a blood sample via venipuncture from all subjects for serological evaluations, according to the Time and Events Table.

e. Administer the randomized subject's group assigned injection in the subject's deltoid muscle: in Group I Men ACWY vaccine will be administered in the right arm and Tdap vaccine in the left arm, in Groups II and III, study vaccine (Men ACWY or Tdap) will be administered into the left arm and saline placebo in the right arm (see directions for Vaccine Administration in Section 6.4.2.3).

f. Give the subject a thermometer to be used for the duration of the study and instruct the subject and subject's parent(s)/guardian(s), when applicable, in its use.

g. At the end of 30 minutes, take the subject's axillary temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject and subjects' parent(s)/guardian(s), when applicable, in completion of the diary card.

h. Dispense subject's diary card for recording daily axillary temperatures, local reactions, systemic reactions, all other AEs, and all concomitant medications. Instruct the subject to notify the site immediately if they experience any SAEs. Instruct the subject on which AEs and concomitant medications should be recorded from after 7 days through Visit 2.

i. Assess best time to call subject 2 and 7 days after injection and schedule subject to return for Visit 2 (28 days + 15 days after Injection).

j. Store sera from all subjects for serology assays.

Telephone Call: Study Day 3 (window: +3 days)

a. Call the subject and subjects' parent(s)/guardian(s), when applicable, and query for SAEs and anything of concern to the subject. Answer any questions the subject and subjects' parent(s)/guardian(s), when applicable, may have about diary card completion. Remind the subject which AEs and concomitant medications to record for the appropriate interval and to record all applicable reactions and AEs on their diary cardRecord the information obtained on the Telephone log.

b. Remind the subject of their next scheduled telephone call.

Telephone Call: Study Day 8 (window: +3 days)

a. Call the subject and subjects' parent(s)/guardian(s), when applicable, and query for SAEs and anything of concern to the subject. Answer any questions the subject and subjects' parent(s)/guardian(s), when applicable, may have about diary card completion. Remind the subject which AEs and concomitant medications to record for the appropriate interval and to record all applicable reactions and AEs on their diary card. Record the information obtained on the Telephone log.

b. Remind the subject of their next scheduled study visit.

Visit 2: Day 29 (window: +15 days)

a. The termination visit will occur on the date the subject withdraws from or completes the study, even if the date does not correspond to a protocol specific visit.

b. In the presence of the subject, review and validate the information reported on the Diary card and the Telephone log. After the reconciliation, recorded the information obtained on the appropriate subject's case report form (CRF).

c. Any ongoing SAEs will be followed to resolution or as deemed appropriate by the investigator and the Novartis (formerly Chiron) medical monitor.

d. Collect blood sample from all subjects for serology assays according to the Time and Events Table.

e. Dispense interim subject memory aid card for recording SAEs and all significant medical events [e.g., AE requiring a physician visit and/or leading to Emergency Room visit (pre-planned visits, medical office visits for routine medical care and common acute conditions, such as upper respiratory tract infections, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, and contact dermatitis will not be collected) and/or resulting in subject's withdrawal from the study and explain how it should be completed.

Telephone Call: Study Day 181 (window: ±15 days)

a. Call the subject and subjects' parent(s)/guardian(s), when applicable, and query for SAEs, medically significant adverse events and anything of concern to the subject.

Answer any questions the subject and subjects' parent(s)/guardian(s), when applicable, may have about memory aid card completion.

b. Ask subjects and/or their parents/legal guardians to return the worksheet to the clinic by mail using a pre-printed envelope. Information from the worksheet will be reported into subject's appropriate CRF.
c. Complete the study termination procedures and complete the study termination CRF.

Following study unblinding, subjects belonging to Group II and III will be respectively offered one single dose of licensed Men C or Td (or Tdap) vaccine, to be administered outside study evaluation and procedures.

6.5.5.1 Study Evaluations

Blood samples will be obtained in the following time windows:

Pre-immunization:	Day 1
Post-immunization:	Day 29 (window: +15 days)

6.5.5.1.1 Laboratory Assessments

No laboratory assessments will be made during this study.

6.5.5.1.2 Labeling and Storage of Serum Samples for Serology

At least 5 mL serum should be available for assays.

The blood will be centrifuged on the same day and the serum will be distributed in 2 aliquots using the tubes provided. The aliquots will be stored at a temperature of minus 18°C or below.

Each serum tube will be labeled with an identifying bar code including protocol number, subject number, subject code, and visit number. Serum samples will be sent to the sponsor or will be collected by a representative of the sponsor upon request.

For further information see Appendix B.

6.6 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained at the latest during the initiation visit. During each monitoring visit source data verification will be performed by qualified staff representing the sponsor. A CRF collation supplied by the sponsor will be completed for each subject. The entries will be checked by trained delegates of the sponsor.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor's CQA department will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms, the Analysis Plan and the Subject Information and Consent Form.

6.6.1 Study Monitoring

The clinical study site will be monitored by regular site visits and telephone calls to the investigator by members of the Clinical Research department, the sponsor, or their agents following Novartis (formerly Chiron)'s internal SOP. For this study, the expected average monitoring frequency is every 5 weeks by personal visit. The first monitoring visit to each investigational site will be performed not later than 7 days after first subject enrollment at the study site. By frequent communication, the site monitor will ensure that the study is conducted according to the protocol.

CRFs and all original data collected at the site should be available for review during monitoring visits. During these visits, the site monitor should review drug accountability records and document retention including the Investigator's Study File. Additionally, the site monitor should check that clinical study procedures are observed and discuss any problems with the investigator.

6.6.2 Source Data Verification and Audits

Inspection and examination of CRFs and source documents (all original recordings, laboratory reports, medical records) - giving due consideration to data protection and medical confidentiality - will be undertaken by representatives of the sponsor. All data not recorded directly on the CRFs as defined in section 6.10 of this study protocol must be verified by checking CRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol. Source data verification will be performed and recorded following Novartis (formerly Chiron) internal SOP. The subject or the subject's legally acceptable representative must also allow access to the subject's medical records. Each subject, or the subject's legally acceptable representative, will be informed of this prior to the start of the study.

During or after the clinical study, the regulatory authorities, the EC or IRB and/or representatives of the sponsor may request access to all source documents, CRFs and other study documentation for on-site audit or inspection.

6.7 Data Management

All CRF data (except for comments fields on the "Medical History" and "Comments" CRFs and the "Other, specify" item on the "Screen Log", if applicable), will be entered in duplicate into a (b) (4) database by BCDM, Novartis (formerly Chiron) .

Data validation will be performed using the programming languages (b) (4) (b) (4) Data quality assurance will be performed by doing a 100% check of all database updates resulting from the resolution of queries, and by estimating the database error rate with 95% upper confidence limit. The latter must be below the departmental accepted level of 0.5%. Analysis will be performed by BCDM using (b) (4) version (b) (4) according to a predefined Analysis Plan (AP), developed by the study Biostatistician.

All serology data analyzed by Clinical Serology, Novartis (formerly Chiron) Vaccines, Marburg will be entered into the (b) (4) database by Clinical Serology, Novartis (formerly Chiron) Vaccines, Marburg. All results will be checked in the laboratory for validity and completeness by 3 persons before access to the data is granted to BCDM.

6.7.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

6.7.2 Data Protection

Novartis (formerly Chiron) respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data [95/46/EC] confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

6.8 Changes in the Conduct of the Study or Planned Analysis

Planned changes in the conduct of the study will be described in protocol amendments; changes in the planned analysis will be described in the clinical study report.

An amendment is a written description of change(s) to or formal clarification of a study protocol.

The EC or IRB must be informed of all amendments and if necessary prior review and documented approval/favorable opinion must be sought for ethical aspects. Approval must also be obtained from the authorities, if necessary.

Such amendment will be agreed upon by the sponsor, the investigator, the EC or IRB, and authorities if necessary prior to implementation.

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical Plans

The statistical evaluation of the results will be performed by BCDM as predefined in the AP. The statistical tables and graphs will be generated using (b) (4) version (b) (4)

Baseline is defined as the time of vaccination.

Definition of populations to be analyzed:

(a) All enrolled population

- all subjects who:
  - have data in the DEMOG panel

Will contain all subjects enrolled in the study, i.e. all subjects who have data in panel DEMOG. This population will be used for the analysis of demographics and all subject listings.

(b) Modified Intention-to-treat (MITT) population, Immunogenicity

- all randomized subjects who:
  - actually receive a study vaccination, and
  - provide at least one evaluable serum sample both before and after baseline

(c) Per protocol (PP) population, Immunogenicity

- all subjects in the MITT population who:
  - receive all the relevant doses of vaccine correctly, and
  - provide evaluable serum samples at the relevant time points, and
  - have no major protocol violation as defined prior to analysis

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

(d) Exposed population

- all enrolled subjects who:
  - actually receive a study vaccination

(e) Safety population

- all subjects in the Exposed population who:
  - provide post-baseline safety data

6.9.1.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group.

6.9.1.2 Analysis of Immunogenicity Criteria

The immunogenicity of the Tdap when given concomitantly with MenACWY (Group I) will be considered non-inferior to that of Tdap when given alone (Group II), if for all five antigens the lower limit of the two-sided 95% confidence interval (CI) for the (Tdap + MenACWY *minus* Tdap) difference in the response percentage will be greater than -10%. (i.e., Tdap + MenACWY *minus* Tdap > -10%).

6.9.1.3 Analysis of Safety Criteria

Number of subjects with reported local and systemic reactions as well as number of subjects with reported serious adverse events and/or all adverse events up to day 7 and/or adverse events requiring a physician visit and/or resulting in premature withdrawal from the study, will be calculated per vaccination group.

Local and Systemic Reactions

Erythema and induration will be categorized as none (0 mm), 1-25 mm, 26-50 mm and >50 mm. Axillary temperature will be categorized as <38°C, 38-38.9 °C, 39-39.9°C and ≥ 40°C. All other systemic reactions will be categorized as none, mild, moderate and severe. Each local and systemic reaction will also be categorized as none vs. any.

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

For the local and systemic reaction safety variables, differences among the vaccine groups after immunization with respect to all variables (including fever) will be analyzed by using Pearson's chi-square test, or Fisher's Exact test where appropriate.

Other Adverse Events

All the adverse events occurring during the study, judged either as related to vaccination or not by the investigator, will be recorded as specified in Section 6.1.1.

The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

6.9.1.4 Interim Analysis Planned

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled "Interim Analysis in a Clinical Trial".

6.9.1.5 Preliminary Analysis

After all subjects have completed Visit 2, a group-unblinded preliminary analysis may be performed to assess immunogenicity.

In addition, an overall preliminary analysis may be performed to assess safety, when all subjects have completed the 7-day follow-up after vaccination (local and systemic reactions and body temperature within 7 days of immunization and SAEs).

The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Novartis (formerly Chiron) BCDM standard operating procedure entitled "Interim Analysis in a Clinical Trial."

6.9.2 Determination of Sample Size

Approximately 1000 healthy subjects aged 11-25 years will be randomized in a 1:1:1 ratio to receive either concomitant administrations of Tdap + Novartis (formerly Chiron) MenACWY vaccines (Group I), or Tdap vaccine + saline placebo (Group II), or Novartis (formerly Chiron) MenACWY vaccine + saline placebo (Group III).

The immunogenicity of the Tdap when given concomitantly with MenACWY (Group I) will be considered non-inferior to that of Tdap when given alone (Group II), if for all five antigens the lower limit of the two-sided 95% confidence interval (CI) for the (Tdap + MenACWY *minus* Tdap) difference in the response percentage will be greater than -10% (i.e., Tdap + MenACWY *minus* Tdap > -10%).

The table below shows, for various underlying response percentages, the power to reject the null hypothesis for each antigen with a one-sided significance level (α) of 0.025. To have at least an overall 80% power for non-inferiority for all five antigens, a power of at least 95.6% for each antigen is needed. (b) (4) version (b) (4) was used to perform the calculations.

Percent of responders Group I Tdap + MenACWY	Percent of responders Group II Tdap	Power to demonstrate non-inferiority for any antigen (N per group = 333 and 1-sided $\alpha = 0.025$)
70%	70%	80%
75%	75%	84%
80%	80%	89%
85%	85%	95%
90%	90%	>99%
95%	95%	>99%

From a perspective of detecting uncommon local or systemic reactions, or AEs, the table below gives the probabilities of observing at least one such event in any vaccine group for several underlying event rates.

Probabilities of Observing at Least One Event

Underlying Event Rate	Probability of observing at least one event in Group II N=333
1/100	96.5%
1/200	81.2%
1/500	48.7%
1/1000	28.3%

6.10 Documentation of Study Findings

A set of CRF collations will be supplied by the sponsor. The CRFs do not require carbon paper. The bottom copy must be retained by the investigator, and all other copies will be returned as directed by the sponsor. Instructions on how to complete these forms will be given to the investigator.

All study findings must be entered by the investigator on these CRFs. If the investigator authorizes other persons to make entries on the CRF, the names, positions, signatures and initials of these persons must be supplied to the sponsor.

All entries in the CRFs must be made *legibly* in black ball-point pen (*not pencil, felt tip or fountain pen*).

The following data may be reported directly on the CRFs and are considered to be source data: demographics data, immunization(s) time, injection(s) site, pre-immunization temperature.

For each enrolled subject a CRF collation must be signed and dated by the investigator named in the study protocol. CRFs must be completed immediately after the final examination. Arrangements will be made by the monitor to collect the CRFs on completion. No CRFs are to be mailed to the sponsor without specific authorization.

A reasonable explanation must be given by the investigator for all missing data.

If corrections are made to entries in the CRF by the investigator or designates, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made after review and signature by the investigator, he/she must be made aware of the changes and document this awareness.

As part of the conduct of the trial, Novartis (formerly Chiron) may have questions about the case report form data after the CRFs are collected from the site. These questions will be documented using Data Clarification Forms (DCFs). Novartis (formerly Chiron) will answer the question if the answer is self-evident on “internal” DCFs, but the investigator will need to review these changes. If the query is not self-evident, Novartis (formerly Chiron) will ask the investigator to provide the answer on an “external” DCF and sign it. Novartis (formerly Chiron) will send the investigator a copy of each completed internal DCF. The investigator will review them and if he/she disagrees with the resolution, he/she will notify the site monitor, who will then generate a new DCF documenting the

investigator's correction. The investigator will be requested to file each of the DCFs (both levels) for the trial.

Definitions of the DCF types are as follows:

Internal DCF: A query for which the resolution is self-evident. It can be answered without changing the meaning of the data (such as moving data from one box to another) or using logical numeric flow (for example, if an adverse event number is missing, the next number in sequence can be assigned). Internal corrections are defined in either the assumptions for internal queries guideline or in study-specific assumptions. The Clinical Data Coordinator or the Clinical Research Associate can answer an internal query. Key safety (e.g. adverse event relationship) or primary endpoint data queries are not to be handled as an internal DCF.

External DCF: A query that requires information from the investigator. Key safety (e.g. adverse event relationship) or primary endpoint data queries must be handled as an external DCF.

6.11 Record Retention

Investigators must retain all study records required by Novartis (formerly Chiron) and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis (formerly Chiron) representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor *or* The Committee for Human Medicinal Products (CHMP) requires retention for the maximum period of time permitted by the institution, but not less than 15 years. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

6.12 Use of Information and Publication

It is understood by the investigator that the information generated in this study will be used by the sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigator is obliged to provide the sponsor with complete test results, all study data, and access to all study records.

The sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences.

Any results of medical investigations with the sponsor products and/or publication/lecture/ manuscripts based thereon, shall be exchanged and discussed by the investigator and the sponsor Clinical Research representative(s) 60 days prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

In cases of publications or presentations of material arising from multicenter clinical investigations, the sponsor is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent and the prior review of the sponsor. In case of disagreement amongst the authors, the sponsor will be the final arbiter. The sponsor comments shall be given without undue delay. If they are not accepted, the senior author of the manuscript and the sponsor's representatives shall promptly meet to discuss further and endeavor to agree mutually on the final wording and/or disposition of the publication. The above procedure also applies to information on prematurely discontinued and other not completed studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The sponsor will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

All information concerning the study drug supplied by the sponsor in connection with this clinical study, and not previously published, is considered confidential and proprietary information. This information includes the Investigator’s Brochure, clinical protocol, workbooks if applicable, CRFs, assay methods, the sponsor’s technical methodology, and basic scientific data. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to others without prior written consent from the sponsor and shall not be used except in the performance of this clinical study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the sponsor in connection with the development of the study drug. This information may be disclosed as deemed necessary by the sponsor.

The investigator is obliged to provide the sponsor with complete test results and all data derived from this clinical study. Only the sponsor may make information obtained during

this clinical study available to the physicians and to the regulatory agencies, except as required by regulation.

7. REFERENCE LIST

1. Rosenstein N, Perkins B, Stephens DS, Popovic T, Hughes J. Meningococcal Disease. N Engl J Med 2001;344(18):1378-88.

2. DeVoe IW. The meningococcus and mechanisms of pathogenicity. Microbiol Rev 1982;46(2):162-90.

3. Andersen BM. Mortality in meningococcal infections. Scand J Infect Dis 1978;10:277-82.

4. De Wals P, Hertoghe L, Reginster G, Borlee I, Bouckaert A, Dachy A, et al. Mortality in meningococcal disease in Belgium. J Infect 1984;8(3):264-73.

5. Halstensen A, Pedersen SH, Haneberg B, Bjorvatn B, Solberg CO. Case fatality of meningococcal disease in western Norway. Scand J Infect Dis 1987;19(1):35-42.

6. Laurichesse H, Grimaud O, Waight P, Johnson AP, George RC, Miller E. Pneumococcal bacteraemia and meningitidis in England and Wales, 1993 to 1995. Commun Dis Public Health 1998;1:22-7.

7. Venetz I, Schopfer K, Muhlemann K. Paediatric, invasive pneumococcal disease in Switzerland, 1985-1994. Swiss Pneumococcal Study Group. Int J Epidemiol 1998;27(6):1101-4.

8. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81(4):536-8.

9. Campagne G, Chippaux JP, Djibo S, Issa O, Garba A. [Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger)]. Bull Soc Pathol Exot 1999;92(2):118-22.

10. Centers for Disease Control and Prevention. Laboratory-based surveillance for meningococcal disease in selected areas--United States, 1989-1991. Morbidity Mortality Weekly Report (MMWR); CDC Surveillance Summaries 1993;42 (SS-2):21-30.

11. Centers for Disease Control and Prevention. Meningococcal disease and college students: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2000;49(RR-7):13-20.

12. Stanwell-Smith RE, Stuart JM, Hughes AO, Robinson P, Griffin MB, Cartwright K. Smoking, the environment and meningococcal disease: a case control study. Epidemiol Infect 1994;112(2):315-28.

13. Vogel U. Meningitis. Outcome of a Complex Interaction. Lancet 2001;358(Suppl):S43.

14. Artenstein MS, Gold R, Zimmerly JG, Wyle FA, Schneider H, Harkins C. Prevention of meningococcal disease by group C polysaccharide vaccine. N Engl J Med 1970;282(8):417-20.

15. Pollard AJ, Frasch C. Development of natural immunity to *Neisseria meningitidis*. Vaccine 2001;19(11-12):1327-46.

16. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med 1969;129:1307-26.

17. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. II. Development of natural immunity. J Exp Med 1969;129:1327-48.

18. Bruce M, Rosenstein N, Capparella J, Shutt K, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. JAMA 2001;286(6)(6):688-93.

19. Amato Neto V, Finger H, Gotschlich EC, Feldman RA, de Avila CA, Konichi SR, et al. Serologic response to serogroup C meningococcal vaccine in Brazilian preschool children. Rev Inst Med Trop Sao Paulo 1974;16(3):149-53.

20. Cadoz M, Armand J, Arminjon F, Gire R, Lafaix C. Tetravalent (A, C, Y, W 135) meningococcal vaccine in children: immunogenicity and safety. Vaccine 1985;3(3):340-42.

21. Peltola H, Safary A, Käyhty H, Karanko V, André FE. Evaluation of two tetravalent ($ACYW_{135}$) meningococcal vaccines in infants and small children: a clinical study comparing immunogenicity of *O*-acetyl-negative and *O*-acetyl-positive group C polysaccharides. Pediatrics 1985;76(1):91-6.

22. Gold R, Lepow ML, Goldschneider I, Draper TF, Gotschlich EC. Kinetics of antibody production to group A and group C meningococcal polysaccharide vaccines administered during the first six years of life: prospects for routine immunization of infants and children. J Infect Dis 1979;140(5):690-7.

23. King WJ, MacDonald NE, Wells G, Huang J, Allen U, Chan F, et al. Total and functional antibody response to a quadrivalent meningococcal polysaccharide vaccine among children. J Pediatr 1996;128(2):196-202.

24. Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. Pediatrics 1977;60(5):673-80.

25. Santosham M. Prevention of *Haemophilus influenzae* type b disease. Vaccine 1993;11(Suppl. 1):S52-7.

26. Shinefield HR, Black S. Efficacy of pneumococcal conjugate vaccines in large scale field trials. Pediatr Infect Dis J 2000;19:394-7.

27. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. Vaccine 2002;20:S58-S67.

28. Ramsay M, Andrews N, Kaczmarski E, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357(Jan 20):195-6.

29. National Advisory Committee on Immunisation (NACI). Statement on recommended use of meningococcal vaccine (Advisory Committee Statement, ACS-6). Canadian Communicable Disease Report--CCDR 2001;27 (15 October 2001).

8. INVESTIGATOR AGREEMENT

INVESTIGATOR AGREEMENT:

I have read the preceding protocol

"A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria and Acellular Pertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, Or One Dose of Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine in Healthy Subjects Aged 11-25 Years"

and received the following:

- Investigator's Brochure with details of pharmacological and toxicological findings with the investigational product, dated 30 November 2004

- ICH Harmonized Tripartite Guideline for Good Clinical Practice".

I have been adequately informed about the development of the investigational product to date. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.

I will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. I will maintain a list of sub-investigators and other appropriate qualified persons to whom I have delegated significant trial-related duties.

I will provide copies of the study protocol and all drug information relating to preclinical and prior clinical experience furnished to me by the sponsor, to all physicians responsible to me who participate in this study. I will discuss this material with them to assure that they are fully informed regarding the vaccine and the conduct of the study.

I will not enroll the first subject in the study until I have received approval from the appropriate EC or IRB, where applicable, and until all legal requirements in my country have been fulfilled.

I will provide a curriculum vitae before the study starts. I agree that these data may be submitted, if necessary, to the relevant authorities. I further agree that my name and contact details and those of my staff will be entered into an electronic study management system maintained by the sponsor for internal use only.

Signing this protocol I agree

- to conduct this clinical study in compliance with ICH GCP, with the applicable regulatory requirement(s), and with the study protocol agreed to by the sponsor and given approval/favorable opinion by the EC or IRB

- to comply with procedures for data recording/reporting

- to permit monitoring, auditing, inspection, and EC or IRB review and

to retain the study related essential documents according to legal requirements and as agreed with the sponsor.

Coordinating Investigator

.....
(print name)

.....
(place, date) (signature)

Principal Investigator

.....
(print name)

.....
(place, date) (signature)

9. SPONSOR AGREEMENT

This study protocol was subject to critical review and has been approved by the appropriate Study Document Review Committee. The information it contains is consistent with:
- Investigator's Brochure with details of pharmacological and toxicological findings with the investigational product, dated: 30 November 2004
- the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and good clinical practice guidelines.
The investigator will be supplied with details of any significant or new findings, including adverse events.

NOVARTIS (formerly Chiron) VACCINES

Head of Clinical Research & Medical Affairs

....
(place, date) Audino Podda

Medical Monitor

....
(place, date) Francesca Ceddia

Study Monitor

....
(place, date) Laura Lauretti

Head of Clinical Biostatistics

....
(place, date) Pantaleo Nacci

Study Biostatistician

....
(place, date) Alessandra Anemona

APPENDIX A
LIST OF CENTRAL LABORATORIES

Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone +49 (0) 6421 39 3439 or 39 3712
Fax. +49 (0)6421-39-5826

APPENDIX B
SHIPPING AND HANDLING OF LABORATORY SPECIMENS

1. Serum must be centrifuged, separated and frozen as soon as possible after collection. Make sure that coagulation is complete before separating the serum from blood components.

2. Please use the cryotubes provided. Be aware that the maximum-fill volume for these tubes is 90 % of rated capacity, i.e., 3.6 mL, to allow for expansion of the frozen serum. The tubes are marked with a maximum-fill line. Other sizes of cryotubes are not acceptable; if you have an inadequate supply, please contact your Monitor and additional tubes will be provided.

3. Close the tubes before freezing, and check to make sure that the caps are completely tight before packing for shipment.

4. Barcode labels are to be placed lengthwise down the tubes (not wrapped around). Barcodes are machine-readable only when their entire length runs along a flat surface. Please do not write on, make markings through, or otherwise deface the barcode. Make sure that labels are securely attached so that they do not pull away from the tubes after freezing. It is not necessary to fasten the label to the tube with adhesive tape.

5. Before the start of the trial, prepare separate cryoboxes for original and duplicate samples (“Original“ and “Duplicate” labeled cryotubes). After serum has been collected, centrifuged and separated, place labeled tubes in the respective labeled cryoboxes “Original“ and “Duplicate”. Keep the tubes in numerical order by subject number.

6. Freeze tubes at ≤ -18 °C (to -80 °C), in an upright position so that serum does not come into contact with the cap. Tubes may be stored in any convenient position once they are frozen. Do not "quick-freeze" tubes by immersing them in either dry ice or liquid nitrogen; this may crack the tubes.

7. Pack cryotubes for shipment according to the instructions provided. If you have questions, please contact your Monitor.

8. Pack the original shipping log in an envelope inside the cardboard shipping box, on top of the Styrofoam insulated shipper and and send it together with the “Original” tubes to the attention of:

Dr. Anne Katrin Hilbert *and/or* Dr. Annette Karsten
Novartis (formerly Chiron) Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 7635041 MarburgGermany

Tel. +49 (0)6421-39-3439/3712
Fax. +49 (0)6421-39-5826

9. The duplicate samples should be sent still frozen after confirming that the first shipment arrived safely.

APPENDIX C
SEROLOGY PROCEDURES

The laboratory procedures for this study will be based on the European "Norm on general criteria for the operation of testing laboratories" (EN 45001).

Retention of Study Records
The analysis protocols, raw data and other documents generated during the course of the study will be retained for 15 years at:
Novartis (formerly Chiron) Vaccines
Klinische Serologie
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone: +49 (0)6421 39 3439/3712

Objectives
Primary: To test human sera for the presence of specific antibodies to:
Antigens: *Diphteria, Tetanus and Pertussis toxin*
Assays: D, T and PT are tested by using an antigen-specific in-house developed ELISA.

Secondary: To test human sera for the presence of bactericidal antibodies to:
Antigens: *Neisseria meningitidis* Serogroup A, C, W_{135}, and Y (b) (4)
Assays: MenA-BCA, MenC-BCA, MenW-BCA, MenY-BCA using human complement.

Sample Storage
Frozen serum samples will be logged and stored at minus 18°Cor below in the Clinical Serology Laboratory, Marburg (see address above).

Test Methods and Procedures

Assay name: Diphtheria-ELISA
Antigen: Diphtheria toxoid
Units: IU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4) IU/mL
Standard: NIBSC standard
Seroconversion/protection limit: ≥ 0,1 IU/mL

Assay name: Tetanus-ELISA
Antigen: Tetanus toxoid

Units: IU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4) IU/mL
Standard: WHO standard
Seroconversion/protection limit: ≥ 0,1 IU/mL

Assay name: Pertussis-toxin ELISA
Antigen: Pertussis toxin
Units: EU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: in-house standard
Seroconversion: 4 fold increase

Assay name: MenA-BCA
Antigen: *Neisseria meningitidis* serogroup A (b) (4)
Units: (b) (4)
Internal Standard / Controls: (b) (4)
Lower Limit of detection : (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenC-BCA
Antigen: *Neisseria meningitidis* serogroup C (b) (4)
Units: (b) (4)
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenW_{135}-BCA
Antigen: *Neisseria meningitidis* serogroup W_{135} (b) (4)
Units: (b) (4)
Internal Standard / Controls: (b) (4)
Lower Limit of detection : (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenY-BCA
Antigen: *Neisseria meningitidis* serogroup Y (b) (4)

Units: (b) (4)
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Equipment
Equipment as listed in the relevant Novartis (formerly Chiron) Serology Laboratory SOP.

Procedures
All procedures will be carried out according to the relevant Novartis (formerly Chiron) Serology Laboratory SOP and associated documents.

CLINICAL STUDY PROTOCOL V59P13

Original Protocol issued 9 October 2006

Amendment No. 1 issued 21 May 2007

Amendment No. 2 issued 20 December 2007

Version number 1 **IND BB-IND 11278**

A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age

SPONSOR	Novartis Vaccines & Diagnostics, Inc. 4560 Horton Street Emeryville, CA 94608-2916
COORDINATING INVESTIGATOR	Lisa Jackson, MD
MEDICAL MONITOR	Jina Shah, MD Phone number: +1(510) 923-5509 Fax number: +1(510) 923-3450
STUDY MONITOR	Tanja Odžak, MS, CRA Phone number: +1(510) 923-3449 Fax number: +1(510) 923-3450
CRO	(b) (4)

For trial related **emergencies out of office hours** please contact: +1(510) 502-3650

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Confidential

May not be used, divulged, published or otherwise disclosed without written consent of Novartis Vaccines & Diagnostics, Inc.

STUDY SYNOPSIS

TITLE OF STUDY:

A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age

INVESTIGATOR (S): Investigators throughout US

STUDY CENTER (S): Multicenter, US

STUDY PERIOD:

Approximately 9 months overall

3 months of enrollment and 6 months of individual subject participation

CLINICAL PHASE: Phase 3

RATIONALE:

Neisseria meningitidis causes life-threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified, with serogroups A, B, C, W_{135} and Y being responsible for the large majority of invasive meningococcal infections worldwide.

Based upon the recent, successful development of conjugate vaccines designed to prevent disease with *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *N. meningitidis*, Novartis Vaccines is developing a conjugate meningococcal ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM_{197} (a non-toxic mutant of diphtheria toxin).

The primary objectives of this phase 3 study are to assess the consistency of the immunogenicity of three manufactured lots of Novartis Meningococcal ACWY conjugate vaccine [MenACWY] when administered to healthy subjects 11-18 years of age, compare the immunogenicity of Novartis Men ACWY (3 lots combined) to Menactra™ in healthy subjects 11-18 years of age, and compare the immunogenicity of Novartis Men ACWY to Menactra™ in healthy subjects 19 to 55 years of age.

MenACWY has been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 2000 subjects have received at least one dose of the final formulation of MenACWY being tested in this study. A comprehensive and detailed review of investigational MenACWY is contained in the Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

OBJECTIVES:

Primary Objectives

Immunogenicity

a. To show the consistency of immune response from three lots of MenACWY, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination with a single dose, when administered to healthy subjects 11 to 18 years of age.

b. To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against N meningitidis serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy adolescents 11 to 18 years of age.

c. To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy adults 19 to 55 years of age.

Safety

To compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY with the percentage of subjects presenting at least one severe systemic reaction to Menactra™ during the first 7 days (Day 1-7) following a single dose administered to healthy subjects (11-55 years of age).

Secondary Objectives

Immunogenicity

a) To assess the consistency of immune response from three lots of MenACWY, as measured by percentage of subjects with seroresponse, hSBA titer $\geq$ 1:4 and $\geq$ 1:8 directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination with a single dose, when administered to adolescents 11 to 18 years of age.

b) To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age.

c) To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of

subjects with hSBA ≥ 1:4 and ≥ 1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age.

d) To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age.

Safety

To describe and compare the percentages of subjects in the MenACWY (3 lots combined) and Menactra vaccine groups when administered to healthy adolescents or adults (11-55 years of age) in terms of:

- Immediate hypersensitivity reactions (within 30 minutes) following vaccination
- Local and systemic reactions during the period Study Day 1 – 7
- Adverse events (AEs) reported during the period Study Day 1- 29
- Medically significant AEs reported during the period Study Day 30 - 180
- Serious adverse events (SAEs) reported from Study Day 1 – 180

METHODS:

This is a phase 3, observer-blind, multi-center, randomized, controlled study in healthy subjects 11-55 years of age.

Subjects will be included in the study if in good health as judged by physical assessment and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 3432 healthy subjects 11-55 years of age will be randomly assigned to receive a single dose of either MenACWY or Menactra. Subjects will be randomized in a 1:1:1:1 ratio to one of four groups (MenACWY lot 1, lot 2, lot 3, or Menactra). Randomization will be stratified by center and age such that 2100 adolescents (11-18 years of age), 400 adults (19-34 years of age) and 932 adults (35-55 years of age) will be enrolled. For all subjects in the 11 to 18 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adolescents as follows. For MenACWY Groups I-III, all 500 evaluable subjects in each group (Lot 1, Lot 2, Lot 3) will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects in each group will have immunogenicity testing performed for serogroups A, W, and Y. For Menactra Group IV, from a randomly selected subset of 220 evaluable Menactra subjects, 220 will have immunogenicity testing performed for serogroups A and C, 190 for serogroup W, and 160 for serogroup Y.

For all subjects in the 19 to 55 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adults as follows. For MenACWY Groups I-III combined, a randomly selected subset of 500 evaluable subjects (from approximately 1000) will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects (from the 500) will have immunogenicity testing performed for serogroups A, W, and Y. For approximately 333 Menactra Group IV subjects in the 19 to 55 years of age group, 233 will have immunogenicity testing performed for serogroups A and C, 190 for serogroup W, and 160 for serogroup Y.

Table 1: Vaccine Group and Immunogenicity Summary

Vaccine Group	Subjects enrolled	Subjects enrolled		
		11-18 yoa*	19-34 yoa**	35-55 yoa**
I MenACWY Lot 1	2574	525	100	233
II MenACWY Lot 2		525	100	233
III MenACWY Lot 3		525	100	233
IV Menactra™	858	525	100	233

*Blood samples will be collected in all adolescents (11-18 years of age) enrolled in Groups I- IV. For all groups, immunogenicity testing will be performed in a randomly selected subset of adolescents as follows. For Groups I-III, 500 evaluable subjects in each group will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects in each group will have immunogenicity testing performed for serogroups A, W, and Y. For Group IV, 500 evaluable subjects will have immunogenicity testing performed for serogroup C, 350 for serogroup A, and 300 for serogroups W and Y.

** Blood samples will be collected in all adults (19-55 years of age) enrolled in Groups I- IV. For all subjects in the 19 to 55 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adults as follows. For MenACWY Groups I-III combined, all subjects will have immunogenicity testing performed for serogroups A and C, and a randomly selected subset of 500 evaluable subjects will have immunogenicity testing performed for serogroups W and Y. For approximately 333 Menactra Group IV subjects in the 19 to 55 years of age group, all will have immunogenicity testing performed for serogroups A and C, and approximately 300 for serogroups W and Y.

At the enrollment visit (**Visit 1, Study Day 1**), the investigator, or a person designated by the investigator, should fully inform the subjects and subjects' parents/legal guardians, as applicable, of all pertinent aspects of the trial and obtained informed consent/assent. An initial physical assessment will be performed and relevant medical history, including the subject's last diphtheria-containing vaccine, if within the past 5 years will be obtained. If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

Subjects will receive either MenACWY or Menactra by an unblinded study vaccine administrator. The subjects will be blinded to the study vaccine given. Subjects in Groups I-III will receive a single dose of one of three lots of MenACWY administered intramuscularly (IM), and subjects enrolled in Group IV will receive a single dose of Menactra (comparator) administered IM. Following vaccination, the subjects will be

monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, and local injection site, and systemic reactions.

Please refer to Table 2 for a summary of relevant medical history, safety assessments, and definitions. See Section 6.5.5 "Study Procedures and Flowchart" for greater detail.

During **Visit 1 (study day 1)**, subjects will be given a Diary Card and instructed on how to complete it for Study Days 1 – 29. In addition, they will be instructed on study procedures.

On **Study Day 3 (study days 3 - 5)**, study site personnel will contact the subject or parents/legal guardians of the subject by telephone to remind them to record reaction data, any other medical problems, and use of concomitant medication on the Diary Card. Sites will record any medical problems reported by the subject and/or parents/legal guardians that are of concern.

On **Study Day 29 (Visit 2, study days 29 - 43)**, all subjects will complete a medical office visit to assess their health status (See Table 1). Sites will perform a physical assessment, including measurement of oral temperature and examination of injection site. Any new adverse findings must be recorded onto the appropriate case report forms (CRFs). The Diary Card given at Visit 1 will be collected and subjects will be given a worksheet and instructed on how to complete it for Study Days 30 - 180.

On **Study Day 180 (study days 165 - 195)**, study site personnel will contact the subject or parents/legal guardians by telephone to assess their health status and review any safety information recorded on the worksheet (see Table 2). They will not be asked to return completed worksheets. Information from the telephone interview will be recorded on the appropriate CRFs.

Table 2: Summary of Relevant Medical History & Safety Assessments

Medical History: Past diagnoses including all allergies, major surgeries requiring in-patient hospitalization, other significant injuries or hospitalizations, any conditions requiring prescription or chronic medication, I.e. >2 weeks in duration or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	
• **Last diphtheria containing vaccination, within the last 5 years**	
Immediate reaction: signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 min after vaccination
Temperature:oral temperature *if fever (≥38 ºC) is persisting beyond Day 7 it will be reported as an AE.*	For 7 days (Day 1 – 7)
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
Systemic reactions: chills, nausea, malaise, myalgia, arthralgia, headache, rash *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
All Adverse Events	For 7 days (Day 1 – 7)
Adverse Events: AEs necessitating a physician's visit and/or resulting in premature study withdrawal	From Day 8 to Day 29
Medically significant AE: **AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal,** with the **exclusion** of pre-planned visits, medical office visits, or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis **(Note, the excluded conditions above will NOT be collected from Day 30 to Day 180)**	From Day 30 to Day 180
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified.If SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 180
Medications: All prescription and non-prescription medications (with the exception of mineral and vitamin supplements)	For 7 days (Day 1 – 7)
Any prescription medications for treatment of reported AEs and chronic medical conditions.	From Day 8 to Day 180
Vaccinations, if any, administered during subject's participation in the study, should be recorded in the subject's CRF	From Day 29 to Day 180

Immunogenicity (All Adolescents and Adults):

At Visit 1 (Day 1), prior to administration of study vaccine, a blood sample (20 ml) will be obtained for serologic evaluation. An additional blood sample (20 ml) will be collected at Visit 2 (Day 29).

NUMBER OF SUBJECTS PLANNED:

Approximately 3432 subjects 11-55 years of age will be randomly assigned to receive either one dose of one of three lots of MenACWY or one dose of Menactra.

SUBJECTS CHARACTERISTICS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Healthy male and female individuals 11-55 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are those:

1. who are 11-55 years of age inclusive and who, after the nature of the study has been explained:
    - have given written assent and/or for whom the parent or legal guardian has provided written informed consent (11-17 years of age)
    - have provided written informed consent (18-55 years of age)
2. who are available for all visits and telephone calls scheduled for the study;
3. who are in good health as determined by:
    - medical history
    - physical assessment
    - clinical judgment of the investigator

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling or unable to give written informed assent or consent to participate in the study;
2. who are perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N. meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
5. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) *(Exception: Receipt of OMP-containing Hib vaccines is permitted)*;

6. who had prior military service
7. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;
8. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within 28 days after vaccination *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination)*
9. who have received a live viral vaccine within 60 days prior to enrollment;
10. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (defined as body temperature ≥38°C) within 3 days prior to enrollment;
11. who have any serious acute, chronic or progressive disease such as
    a. history of cancer (excluding minor non-melanoma skin cancer)
    b. complicated diabetes mellitus
    c. advanced arteriosclerotic disease
    d. autoimmune disease
    e. HIV infection or AIDS
    f. blood dyscrasias
    g. congestive heart failure
    h. renal failure
    i. severe malnutrition

    (Note: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment);
12. who are pregnant or nursing (breastfeeding) mothers (Females will have a urine pregnancy test at entry, sensitive to 20 IU β-hCG)
13. If female of childbearing potential and sexually active with a male partner, has not used or does not plan to use acceptable birth control measures detailed in the section entitled “Females of childbearing potential” at least 30 days before study entry and continuing through 180 days after the last vaccine dose.

Females of Childbearing Potential

Non-childbearing potential is defined as menopausal for at least 1 year or status post surgical sterilization, i.e. bilateral tubal ligation, bilateral oophorectomy, or hysterectomy. A urine pregnancy test will be performed on all female subjects on the same day as and prior to vaccination (Day 1, Visit 1).

Females of childbearing potential (i.e., not surgically sterile or at least 1 year postmenopausal) must have utilized one of the following methods of birth control for at least 30 days prior to study entry and agree to continue utilizing the same method of birth control for at least 180 days after vaccination:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant, vaginal ring);
- Barrier method (such as condom with spermicide or diaphragm with spermicide) each and every time during intercourse;
- Intrauterine device (IUD);
- Monogamous relationship with vasectomized partner.

14. who have epilepsy or any progressive neurological disease or history of Guillain Barré Syndrome;
15. who have a history of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
16. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
    - receipt of immunostimulants
    - receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 90 days prior to enrollment and for the full length of the study
17. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
18. who have Down's syndrome or other known cytogenic disorders;
19. who are planning to leave the area of the study site before the end of the study period.
20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore a blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

TEST VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

The investigational Novartis meningococcal ACWY conjugate vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component with the Men CWY full liquid vaccine.

After reconstitution, MenACWY will have the following composition per 0.5 mL of injectable solution (See Table 3):

Table 3: MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

One 0.5 mL dose of MenACWY will be administered by intramuscular (IM) injection in the left deltoid area.

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Licensed meningococcal ACWY conjugate vaccine Menactra™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single 0.5 mL dose formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. (See Table 4)

Table 4: Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	4 µg
Serogroup C polysaccharide (PS)	4 µg
Serogroup Y polysaccharide (PS)	4 µg
Serogroup W135 polysaccharide (PS)	4 µg
Diphtheria toxoid protein total (Each PS is conjugated to diphtheria toxoid)	48 µg
Sodium phosphate	(b) (4)
Sodium chloride	(b) (4)

One 0.5 mL dose of Menactra will be administered by IM injection in the left deltoid area.

NOTE: Because study and control vaccines have different appearance in the syringe and different reconstitution requirements vaccinations and safety assessments each will be performed by different study personnel to ensure blinding.

CONCOMITANT VACCINES:

No concomitant vaccines will be administered during Visit 1.

The following vaccines are allowed if given at least 29 days after study vaccination and after the Visit 2 blood draw:

- Normal routine or catch-up vaccinations appropriate for this age group
- Recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination).*

Vaccinations will be reported as concomitant medications on the subject's CRF.

MEASURES OF IMMUNOGENICITY:

The ability of MenACWY to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Activity, hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed.

MEASURES OF SAFETY:

The measures of safety to be used in this study consist of local and systemic reactions and other adverse events.

SEROLOGY:

The SBA analyses will be performed at:

Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone: +49 (0) 6421 39 3439/3712

Other laboratories may be employed, as directed by the sponsor.

CRITERIA FOR ASSESSING IMMUNOGENICITY OBJECTIVES:

Primary

a) Immunogenicity of the 3 lots of MenACWY will be considered equivalent if for each serogroup and each pair of vaccine lots, the two-sided 95% CI on the ratio of GMTs at 1 month after the vaccination is contained within the interval [0.50, 2.00].

b) Immunogenicity of MenACWY (pooling of Groups I, II, III) will be considered non-inferior to the immunogenicity of Menactra (Group IV) in the 11 to 18 yoa and 19 to 55 yoa groups, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (MenACWY minus Menactra) is greater than -10%. The statistical superiority of MenACWY in comparison to Menactra will also be assessed for any given serogroup. A MenACWY serogroup will be considered to have a statistically significant higher immune response compared to that same serogroup of Menactra if the lower limit of the two-sided 95% CI around the difference in percentage of subjects with seroresponse (MenACWY minus Menactra) is greater than 0, i.e., the CI does not include zero. The combined hypothesis testing for non-inferiority and statistical superiority does not require any adjustment for multiplicity.

The success criteria for this study is a composite based upon both co-primary objectives: lot-to-lot consistency for the three MenACWY lots and seroresponse non-inferiority of MenACWY as compared to Menactra. Novartis will consider this study a success if all 20 of the analyses (4 serogroups * 3 pairs of lots for the ratio of GMTs plus 4 serogroups * 2 age groups for the MenACWY:Menactra seroresponse comparison) meet the criteria specifically identified for the respective endpoints noted above.

Secondary

Immunogenicity of MenACWY (pooling of Groups I, II, III) will be considered non-inferior to the immunogenicity of Menactra™ (Group IV), in the 11 to 55 yoa group, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥ 1:8 (or hSBA ≥1:4) for that serogroup (MenACWY minus Menactra™) is greater than -10%. The superiority of MenACWY in comparison to Menactra™ will also be assessed for any given serogroup. A MenACWY serogroup will be considered to have a statistically significant higher immune response compared to that same serogroup of Menactra™ if the lower limit of the two-sided 95% CI around the difference in percentage of subjects with hSBA ≥ 1:8 (or hSBA ≥1:4) (MenACWY minus Menactra™) is greater than 0, i.e., the CI does not include zero. The combined hypothesis testing for non-inferiority and statistical superiority does not require any adjustment for multiplicity.

The immunogenicity response of MenACWY (pooling Groups I, II, and III) will be considered non-inferior to the immunogenicity of Menactra, in the 11 to 55 yoa group, if the lower limit of the two-sided 95% confidence interval (CI) around the ratio of hSBA GMTs between MenACWY and Menactra, one month after vaccination, is above 0.5.

CRITERIA FOR ASSESSING SAFETY OBJECTIVES:

MenACWY will be considered non-inferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% confidence interval of the difference ($p_{MenACWY}$ - $p_{Menactra}$) is less than 6%, where $p_{MenACWY}$ and $p_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1 – Day 7) after vaccination with MenACWY (pooling of Groups I, II, III) and Menactra (Group IV), respectively.

STATISTICAL HYPOTHESIS:

Immunogenicity

Primary

a) The null hypothesis associated with the lot-to-lot immunogenicity objective is that for at least one pair of MenACWY lots and for at least one serogroup, the two-sided 95% CI on the ratio of hSBA GMTs at one month after the vaccination is outside the interval [0.50, 2.00].

b) The null hypothesis associated with the non-inferiority immunogenicity objective in the 11 to 18 yoa adolescent group is that for at least one serogroup, the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (e.g., MenACWY {pooling of Groups I, II, III} *minus* Menactra {Group IV}) is ≤ -10%.

c) The null hypothesis associated with the non-inferiority immunogenicity objective in the 19 to 55 yoa adult group is that for at least one serogroup, the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (e.g., MenACWY {pooling of Groups I, II, III} minus Menactra {Group IV}) is ≤ -10%.

Secondary

a. A null hypothesis associated with the secondary lot-to-lot immunogenicity objective is that for at least one pair of MenACWY lots and for at least one serogroup, the two-sided 95% CI on the difference in proportions of responders (seroresponse or hSBA titers ≥1:8) at one month after vaccination is outside the interval (-10%, 10%).

b. The null hypothesis associated with the non-inferiority immunogenicity objective (e.g., secondary objective (c)) is that for at least one serogroup, the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥ 1:8 (or hSBA ≥1:4) for that serogroup (e.g., MenACWY {pooling of Groups I, II, III} *minus* Menactra™ {Group IV}) is ≤ -10%.

c. The null hypothesis associated with the GMT-based non-inferiority objective is that, for at least one serogroup, the lower limit of the two-sided 95% CI of the ratio of GMTs between MenACWY and Menactra, one month after vaccination, is ≤ 0.5.

Safety

Primary

The null hypothesis associated with the primary safety objective is that the upper limit of the two-sided 95% confidence interval of the difference ($p_{MenACWY}$ - $p_{Menactra}$) is ≥6%, where $p_{MenACWY}$ and $p_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1 – Day 7) after vaccination with MenACWY (pooling of Groups I, II, III) and Menactra (Group IV), respectively.

STATISTICAL POWER CONSIDERATIONS:

Immunogenicity

PrimaryLot-to-Lot Consistency

The within group standard deviation for the log10 hSBA titers was assumed equal to 0.73 for serogroup A, 1.06 for serogroup C, 0.65 for serogroup W, and 0.80 for serogroup Y. These estimates were obtained, respectively, as the square root of the upper limit of the 80% CI of the within group variance observed for each serogroup in the previous Novartis MenACWY V59P6 study. The power to reject the null hypothesis associated with the primary immunogenicity objective is the probability that, for each serogroup, for all three pairs of MenACWY vaccine lots simultaneously, the two-sided 95%confidence interval (CI) for the ratio of GMTs at 1 month after vaccination is entirely contained within the interval [0.50, 2.00]. For each serogroup, using the standard deviations given above, the power (and also sample sizes) was approximated by performing 5000 simulations for underlying GMT ratios (r) ranging from 1.0 to 1.6. (See Tables 5 and 6 below). In each replication, three independent samples were drawn from normal distributions with means log10(r), {log10(r)}/2, and 0, respectively, with the common standard deviation for that serogroup. For example, the simulated power for each serogroup to rule out a 2-fold difference was computed as the percentage of replications in which, for all three pairs of vaccine lots simultaneously, the 95% CI was contained within the interval [0.5, 2.0].

Table 5: Sample Size Per Group (Obtained by Simulation) to Achieve 80% or 90% Power for 95% CIs of the Ratio of GMTs from All Three Lots to be Contained Within [0.5, 2.0] by Serogroup and Underlying GMT Ratio

Serogroup	Highest:Lowest GMT Ratio	N Per Group for 80% Power	N per Group for 90% Power
A	1.0	160	190
	1.2	200	250
	1.4	360	470
	1.6	900	1200
C	1.0	340	400
	1.2	420	530
	1.4	750	1000
	1.6	1900	2500
W	1.0	130	150
	1.2	160	200
	1.4	280	370
	1.6	710	950
Y	1.0	200	230
	1.2	240	300
	1.4	440	550
	1.6	1100	1400

From Table 5 above, the sample size to achieve 90% power is much higher for serogroup C than for A, W, and Y. In order to ensure high power for serogroup C, 525 subjects will be randomized to each of the 3 MenACWY lots to obtain 500 evaluable subjects. In order to maintain the 1:1:1:1 treatment group balance in the randomization, 525 Menactra subjects will also be enrolled. In addition, in order to conserve human complement donor resources for A, W, and Y, it was decided to assay a smaller number of evaluable subjects for each of these serogroups. Table 6 below shows the power for various sample sizes per group by serogroup and underlying GMT ratios, and overall power for the 95% CIs of the ratio of GMTs from all three pairs of lots to be contained within [0.5, 2.0].

Table 6: Power (Obtained by Simulation*) for Various Sample Sizes Per Group by Serogroup and Underlying GMT Ratios, and Overall power for the 95% CIs of the Ratio of GMTs from All Three Lots to be Contained within [0.5, 2.0]

		Power for Each Serogroup Using Simulation of Three Tests				
Sample Size Per Group	Highest:Lowest GMT Ratio	A	C	W	Y	Overall Power
250	1.0	0.9740	0.5568	0.9958	0.9296	0.5020
	1.2	0.8928	0.4366	0.9592	0.8090	0.3025
	1.4	0.6232	0.2512	0.7402	0.5270	0.0611
	1.6	0.3016	0.1140	0.3822	0.2468	0.0032
300	1.0	0.9942	0.7170	0.9992	0.9784	0.6969
	1.2	0.9476	0.5684	0.9852	0.8896	0.4721
	1.4	0.7156	0.3410	0.8136	0.6276	0.1246
	1.6	0.3524	0.1478	0.4438	0.2926	0.0068
350	1.0	0.9986	0.8226	0.9999	0.9916	0.8145
	1.2	0.9736	0.6854	0.9932	0.9440	0.6257
	1.4	0.7880	0.4076	0.8740	0.6952	0.1952
	1.6	0.4044	0.1774	0.4990	0.3330	0.0119
400	1.0	0.9992	0.8912	0.9999	0.9978	0.8884
	1.2	0.9892	0.7748	0.9978	0.9678	0.7401
	1.4	0.8504	0.4810	0.9212	0.7782	0.2932
	1.6	0.4624	0.2170	0.5548	0.3898	0.0217
450	1.0	0.9998	0.9430	0.9999	0.9990	0.9418
	1.2	0.9968	0.8256	0.9996	0.9866	0.8116
	1.4	0.8856	0.5342	0.9428	0.8248	0.3679
	1.6	0.5062	0.2446	0.6048	0.4286	0.0321
500	1.0	0.9999	0.9694	0.9999	0.9998	0.9690
	1.2	0.9976	0.8742	0.9994	0.9916	0.8643
	1.4	0.9180	0.5978	0.9658	0.8596	0.4556
	1.6	0.5520	0.2782	0.6502	0.4784	0.0478

*****Uses simulation to calculate the power of the three tests for equivalence (lot 1 vs. lot 2, lot 1 vs. lot 3, lot 2 vs. lot 3) for each serogroup, and then multiplies the results over the four serogroups for the overall power.

With 500 evaluable subjects per lot assayed for serogroup C, and 350 evaluable subjects per lot assayed for serogroups A, W, and Y, the power to reject the null hypothesis associated with the primary lot-to-lot immunogenicity objective and demonstrate immunologic consistency for each serogroup is 97%, >99%, >99%, >99% for C, A, W, and Y, respectively. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic consistency is equal to 96%.

Primary Seroresponse

The estimate of the percentage of subjects with seroresponse for each serogroup as observed in the previous Novartis MenACWY V59P6 study in adolescents 11-17 yoa is shown in Table 7 below.

Table 7: Percentage of subjects for each serogroup with Seroresponse as observed in Novartis study V59P6

	Seroresponse	
Serogroup	MenACWY N=147-148	Menomune N=152-158
A	81%	41%
C	75%	54%
W	85%	71%
Y	86%	66%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in Rabbit Complement SBA (rSBA) and in terms of GMTs.

Given the results in Table 7 we can assume that, for each serogroup, the percentage of subjects with seroresponse is 0%, 5%, or 10% higher in the MenACWY group compared to Menactra. Table 8 below shows, for each serogroup, the number of subjects that will be tested by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 8: Number of Subjects to be Tested by hSBA for 90% Power to Demonstrate Non-inferiority for Serogroups A,C,W and Y, Given Estimated Percent of Subjects with Seroresponse in MenACWY and Menactra Groups

Serogroup	Percent of subjects with Seroresponse MenACWY group (pooling of Groups I, II, III)	Percent of subjects with Seroresponse Menactra group (Group IV)	Number of subjects evaluated in each group in order to have 90% power
A	76%	76%	384
	81%	76%	158
	86%	76%	80
C	70%	70%	442
	75%	70%	186
	80%	70%	98
W	80%	80%	337
	85%	80%	135
	90%	80%	66
Y	81%	81%	324
	86%	81%	129
	91%	81%	62

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%

Table 9 below shows the power for given sample sizes to demonstrate non-inferiority for serogroups A, C, W, Y given estimated percentages of subjects with seroresponse in the MenACWY and Menactra groups. In the MenACWY group there will be 1500 subjects with results for serogroup C, and 1050 subjects with results for serogroups A, W, and Y.

Table 9: Sample Sizes in the Menactra Group to Demonstrate Non-Inferiority with Approximately 99% Power for Serogroups A, C, W, Y Given Estimated Percentage of Subjects with Seroresponse in MenACWY and Menactra Groups

	MenACWY Group (Groups I, II, III Pooled)		**Menactra Group (Group IV)**		
Serogroup	Percentage with Seroresponse	N / Group	Percentage with Seroresponse	N / Group	Power for Non-Inferiority
A	76%	1050	76%	500	99%
	81%	1050	81%	350	99%
	81%	1050	76%	220	99%
	86%	1050	76%	110	99%
C	70%	1500	70%	500	99%
	75%	1500	75%	500	99%
	75%	1500	70%	220	99%
	80%	1500	70%	120	99%
W	80%	1050	80%	500	99%
	85%	1050	85%	300	99%
	85%	1050	80%	190	99%
	90%	1050	80%	100	99%
Y	81%	1050	81%	470	99%
	86%	1050	86%	300	99%
	86%	1050	81%	160	99%
	91%	1050	81%	85	99%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

To be conservative, we can assume that, for each serogroup, the percentage of subjects in the 11 to 18 yoa adolescent group with seroresponse is similar in the MenACWY group compared to Menactra. From Table 9 above, with 1500 evaluable subjects assayed for MenACWY serogroup C, 1050 evaluable subjects assayed for MenACWY serogroups A, W, and Y, 350 evaluable subjects assayed for Menactra serogroup A, 500 evaluable subjects assayed for Menactra serogroup C, and 300 subjects assayed for Menactra serogroups W and Y, the power to reject the null hypothesis associated with the non-inferiority immunogenicity primary objective and demonstrate non-inferiority for each serogroup is 99% for each of the serogroups A, C, W, and Y. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority is equal to 96%.

Applying the same assumptions used for the 11 to 18 yoa adolescent group to the 19 to 55 yoa adult group, the overall power to demonstrate immunologic non-inferiority in the 19 to 55 yoa age adult group is estimated to be 90%. The estimate of the overall power across the three primary objectives is 83% (=96% X 96% X 90%).

Secondary

Table 10 below shows the power to demonstrate, simultaneously, for a given serogroup that for each of the 3 pairs of lots the 95% confidence intervals for the difference in percentage responders between the lots is within (-10%, 10%).

Table 10: Power to Demonstrate that for Each Pair of Lots the 95% C.I. for the Difference in Percentage of Responders (hSBA ≥ 1:8) Between the Lots is within (-10%, 10%) for Underlying Event Rates of 70% to 90%

Underlying Event Rate (hSBA ≥ 1:8)	Simulated Power for Three Lots with		
	N=350 per Lot	N=400 per Lot	N=500 per Lot
70%	39%	52%	71%
75%	49%	61%	80%
80%	63%	75%	89%
85%	81%	89%	97%
90%	96%	98%	>99%

The estimate of the percentage of subjects with hSBA ≥1:8 for each serogroup as observed in the previous Novartis MenACWY V59P6 study in adolescents 11-17 yoa is shown in Table 11 below.

Table 11: Percentage of subjects with hSBA ≥1:8 for each serogroup as observed in Novartis V59P6 study

	% hSBA≥1:8	
Serogroup	MenACWY N=147-148	Menomune N=152-158
A	81%	41%
C	83%	62%
W	90%	84%
Y	95%	82%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in rSBA and in terms of GMTs.

Given the results in Table 11, and assuming that the percentage of subjects with hSBA≥1:8 is 0%, 5%, or 10% higher in the MenACWY group compared to Menactra for serogroup A and C, and is 0%. 2%, or 4% higher in the MenACWY group compared to Menactra for serogroup W and Y, Table 12 below shows the number of subjects to be evaluated by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 12: Number of subjects to be tested by hSBA for 90% power to demonstrate non-inferiority for serogroups A,C,W and Y, given estimated percent of subjects with hSBA≥1:8 in hSBA in MenACWY and Menactra groups

Serogroup	Percent of subjects with hSBA≥1:8 MenACWY group (pooling of Groups I, II, III)	Percent of subjects with hSBA≥1:8 Menactra group (Group IV)	Number of subjects evaluated in each group in order to have 90% power
A	76%%	76%	384
	81%	76%	158
	86%	76%	80
C	78%	78%	361
	83%	78%	147
	88%	78%	73
W	90%	90%	190
	92%	90%	120
	94%	90%	79
Y	93%	93%	137
	95%	93%	83
	97%	93%	51

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%.

Employing the serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs), immunogenicity of the MenACWY group (Groups I, II, and III combined) will be considered non-inferior to the immunogenicity of the Menactra group if the lower limit of the two-sided 95% confidence interval of the ratio of the MenACWY to Menactra GMTs, as measured by hSBA, is ≥0.5 at one month after vaccination, when administered to healthy subjects 11 to 55 years of age. The same within group standard deviations as used for the lot-to-lot comparisons are assumed here.

Table 13 below shows the power to demonstrate non-inferiority for this secondary objective for each serogroup using the standard deviations for each serogroup, highest:lowest GMT ratio, and sample sizes determined above for testing the primary null hypotheses.

Table 13: Power Calculations for Showing Non-Inferiority of MenACWY to Menactra Using the Lower Limit of the Two-Sided 95% CI on the ratio of the MenACWY to Menactra hSBA GMTs for Each Serogroup

Serogroup	Highest:Lowest GMT Ratio	MenACWY N Per Group	Menactra N Per Group	Power for Non-Inferiority
A	1.0	1400	450	99%
	1.2	1400	450	99%
C	1.0	2000	450	99%
	1.2	2000	450	98%
W	1.0	1400	380	99%
	1.2	1400	380	99%
Y	1.0	1400	320	99%
	1.2	1400	320	99%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

With the large number of evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity secondary objective for hSBA GMTs and demonstrate non-inferiority is greater than 99% for all serogroups, assuming a true underlying highest: lowest GMT ratio of 1.

Safety

The primary safety null hypothesis is that the upper limit of the two-sided 95% confidence interval for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra ($p_{MenACWY} - p_{Menactra}$) is ≥6%. Assuming a sample size of 2574 subjects (11-55 years of age) in the MenACWY group (pooling of Groups I, II, III) and 858 subjects (11-55 years of age) in the Menactra group (Group IV) and a percentage of subjects experiencing at least one severe systemic reaction equal to 5% in both groups, the power to demonstrate non-inferiority for safety is equal to 99%. (α=0.025).

From a perspective of detecting uncommon local or systemic reactions, or AEs, Table 14 (below) gives the probabilities of observing at least one subject with one such event for either vaccine group for several underlying event rates.

Table 14: Probability of Observing at Least One Subject with an Uncommon Event in the MenACWY and Menactra groups for Given Underlying Event Rates

Underlying Event Rate	Probability of observing at least one event in Group I, II, or III (MenACWY) N=2574	Probability of observing at least one event in Group IV (Menactra) N=858
1/100	>0.99	>0.99
1/200	>0.99	0.99
1/500	0.99	0.82
1/1000	0.92	0.58

INTERIM ANALYSIS:

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled "Interim Analysis in a Clinical Trial".

After all subjects have completed Visit 2, (one month after vaccination), a group unblinded analysis may be performed to assess immunogenicity.

In addition, a preliminary analysis may be performed to assess safety after all subjects have completed Visit 2 (one month visit after vaccination, including local and systemic reactions and body temperature within 7 days of immunization).

The results of these analyses will not alter the course of the trial.

Table 14: TIME AND EVENTS

Visit Number	**1**	☎	**2**	☎
Study Day (window)	Day 1	Day 3 (Study days 3 – 5)	Day 29 (Study days 29 to 43)	Day 180 (Study days 165 – 195)
Obtain Informed consent/assent	X			
Medical History	X			
Physical Assessment [a]	X		X	
Obtain Blood Sample	X		X	
Administer Study Vaccine [b]	X			
Injection-site Examination	X [b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications [c, d]	X		X	X
Serious Adverse Events [e]	X	X	X	X
Study Termination				X

Note: Day 1 is defined as day of study vaccination.

[a] The physical assessments at Visit 1 (study day 1) should be performed by a study physician or designee.
[b] All subjects will be observed in the clinic for 30 minutes after vaccination.
[c] Collect data on concomitant medications prescription and non prescription through the first 7 days.
[d] Collect data on concomitant medications (prescriptions only) from Day 8 through Day 180.
[e] Collect information regarding any SAE or any event resulting in a subject's early termination at any time during the subject's study participation. A 6-month follow up call will be made to assess the occurrence of SAEs and significant medical events (Please see definitions on Table 2.)

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse Event
AP	(Statistical) Analysis Plan
BCDM	Biostatistics and Clinical Data Management
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EDT	Electronic Data Transfer
EC	Ethics Committee
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
hSBA	Human Serum Bactericidal Activity
HIPAA	Health Insurance Portability and Accountability Act
HiB	*Haemophilus Influenzae* Type B
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization

IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal ACWY Conjugate Vaccine
MITT	Modified Intention-To-Treat
OMP	Outer Membrane Protein
PP	Per Protocol
qs	Quantity Sufficient
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
WFI	Water For Injection
WHO	World Health Organization
yoa	Years of Age

Definitions of Terms

End of Trial: The End of Trial corresponds to the last visit of the last subject undergoing the trial (LSLV, Last Subject Last Visit).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. Novartis Vaccines & Diagnostics, Inc. is an affiliate of Novartis AG.

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an

investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

Local and Systemic Reactions: Selected local and systemic AEs are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within seven days after immunization are herein termed "local and systemic reactions."

Month, Day: Study months are based upon 28-day cycles. The study day refers to the number of days after enrollment, with the day of first vaccination being designated day 1.

Serious Adverse Event: Any experience or reaction that suggests a significant hazard, contraindication, side effect, or precaution. These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital abnormality, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate medical judgment, may jeopardize the subject. Vaccine failure should also be considered as a serious adverse event (SAE).

Medical Monitor: The Medical Monitor is a physician designated by Novartis Vaccines to be readily available to advise on trial related medical questions or problems and provide the appropriate medical expertise on behalf of the sponsor required for the design and conduct of the trial.

Clinical Research Associate/Field Monitor/Study Monitor: The person authorized by Novartis Vaccines to monitor clinical trial activities at the trial site. Study Monitor and Clinical Research Associate are used synonymously.

2. ETHICS

2.1 Approval of Study Protocol

Novartis Vaccines or the investigator will provide the ethics committee (EC) or institutional review board (IRB) with all appropriate material, including the informed consent document, according to the local regulation. The EC or IRB should also be asked for a written statement regarding the composition of the committee and should comply with GCP and with the applicable regulatory requirement(s). The trial will not be initiated until appropriate EC or IRB approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. Prior to enrollment, the sponsor and the investigator must exchange written confirmation that their ethical and legal responsibilities have been observed. The EC or IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. Appropriate reports on the progress of the study will be made to the EC or IRB and the sponsor by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the sponsor.

2.2 Ethical Conduct and Good Clinical Practice

This trial will be performed with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study is conducted., and applicable standard operating procedures (SOPs). Specifically, this trial is based on adequately performed laboratory and animal experimentation; the trial will be conducted under a protocol reviewed and approved by an EC or IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed. A copy of the ICH GCP guidelines and of the Declaration of Helsinki will be included in the investigator's study file.

2.3 Informed Consent of Subject and Confidentiality

2.3.1 Informed Consent of Subject

Adult subjects:

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject’s legal rights the information should include that access to original medical records and processing of coded personal information must be authorized. A

person who is qualified, according to applicable local regulations, must conduct the informed consent discussion. The subject should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

If a subject is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject's rights was accurately explained to, and apparently understood by the subject and that informed consent was given freely.

The investigator will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator's study file.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive EC's or IRB's approval before use.

The subject should be informed in a timely manner if new information becomes available that might affect the decision to participate in the clinical trial. The communication of this information should be documented.

Incapacitated adults:

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. The information about the trial must be given orally and in an understandable form to the legally acceptable representative. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights the information should include that access to original medical records and processing of coded personal information must be authorized. A person who is qualified according to applicable local regulations must conduct the informed consent discussion. The subject's legally acceptable representative should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject's legally acceptable representative and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

In addition, the subject should be informed about the trial according to his or her capacity of understanding. Oral and written information is provided. If possible, the subject should sign and personally date a written informed consent as affirmatively agreement to

participate in the clinical trial. Depending on the subject's capability of assessing the given information and forming an opinion the subject's explicit wish to refuse participation must be respected, even if the legally acceptable representative gives consent. This applies also to the wish to withdraw from the trial.

If the subject or his/her legally acceptable representative is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject or his/her legally acceptable representative has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject's rights were accurately explained to, and apparently understood by the subject or the legally acceptable representative and that informed consent was given freely.

The investigator will provide a copy of the signed informed consent documents to the subject's legally acceptable representative, and will maintain the original(s) in the investigator's study file.

The written informed consent form and any other written information should be revised whenever important new information becomes available that may be relevant to the legally acceptable representative's and subject's consent. Any revised written informed consent form, and written information should receive EC's or IRB's approval before use.

The subject and the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

2.3.2 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor. Study findings stored on a computer will be subject to local data protection laws. The subject, or where applicable, the subject's legally acceptable representative(s) will be informed that representatives of the sponsor, EC or IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

The investigator or designee will maintain a personal list of subject numbers and subject identification codes to enable records to be found at a later date.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to trial initiation, the investigator at the site must provide to Novartis Vaccines & Diagnostics, Inc. a fully executed and a signed financial disclosure form. Financial Disclosure Forms must also be completed for all sub investigators listed on the Form 1572 who will be directly involved in the treatment or evaluation of research subjects in this trial.

The trial will be administered and monitored by employees or representatives of Novartis Vaccines. Study Monitors or Field Monitors will monitor the site on a periodic basis and perform verification of source documentation for each subject. The Medical Monitor will be readily available to provide appropriate medical expertise on trial related medical questions. Novartis Vaccines & Diagnostics, Inc Regulatory Affairs or Pharmacovigilance Department will be responsible for the timely reporting of serious adverse events (SAEs).

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Contract Research Organization

(b) (4)

4. INTRODUCTION

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease causes high rates of morbidity and mortality even among patients who receive early antibiotic treatment. Meningococcal meningitis has a case fatality rate of 5% to 10%, and in meningococcal septicemia fatality rate can be as high as 20% to 40%. (1, 2, 3, 4, 5, 6)

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of N. meningitidis have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, Y, and W-135 being responsible for the large majority of invasive meningococcal infections worldwide (4, 5, 7, 8, 9, 10, 11). The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. (12, 13) Currently there is no licensed vaccine in the United States for serogroup B, while there is an ACWY meningococcal polysaccharide vaccine, Menomune® (Sanofi Pasteur), licensed for use in children ≥ 2 years of age and an ACWY meningococcal conjugate vaccine, Menactra™ (Sanofi Pasteur), licensed for use in adolescents ≥ 11 years of age. As the polysaccharide vaccine induces a largely T-cell independent immune response, the duration of protection is limited (e.g., 2 to 4 years), and hyporesponsivness to repeated doses has been described. (14, 15, 16, 17)

Based upon the recent, successful development of conjugate vaccines designed to prevent disease with *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *N. meningitidis* serogroup C, Novartis is developing a conjugate meningococcal ACWY vaccine (MenACWY) for use in infants through adults. (18, 19) This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, Y, and W conjugated to a protein carrier CRM_{197} (a nontoxic mutant of diphtheria toxin).

Phase II studies of the MenACWY conducted in infants in Canada and the UK have demonstrated that the vaccine is well tolerated and highly immunogenic following two or three doses administered during their routine infant vaccination schedule. MenACWY has also been tested in older age groups and has been shown to be well tolerated and immunogenic. Overall, more than 2000 subjects (from infants through adolescents) have received at least one dose of the final formulation of MenACWY being tested in this study.

The primary objective of this phase 3 study is to show the consistency of immune response from three lots of MenACWY, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against N meningitidis serogroups A, C, W-135, and Y, when administered to healthy subjects 11 to 18 years of age at one month after vaccination with a single dose. The study is also designed to demonstrate, as additional primary objectives, that the immunogenicity of MenACWY in not inferior to that of Menactra as measured by seroresponse at 1 month after vaccination in healthy subjects ages 11 to 18 and 19 to 55 years old. A comprehensive and detailed review of investigational MenACWY is contained in the

Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

5. STUDY OBJECTIVES

5.1 Primary Objectives

Immunogenicity

a) To show the consistency of immune response from three lots of MenACWY, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination with a single dose, when administered to healthy subjects 11 to 18 years of age.

b) To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against N meningitidis serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy adolescents 11 to 18 years of age

c) To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against N meningitidis serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy adults 19 to 55 years of age

5.2 Secondary Objectives

Immunogenicity

a. To assess the consistency of immune response from three lots of MenACWY, as measured by percentage of subjects with seroresponse, hSBA titer ≥ 1:4 and ≥ 1:8 directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination with a single dose, when administered to adolescents 11 to 18 years of age.

b. To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age

c. To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8 directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age.

d. To compare the immunogenicity of a single dose of MenACWY (3 lots combined) with the immunogenicity of a single dose of Menactra, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 11 to 55 years of age.

5.3 Safety Objectives

Primary

To compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY with the percentage of subjects presenting at least one severe systemic reaction to Menactra™ during the first 7 days (Day 1-7) following a single dose administered to healthy subjects (11-55 years of age).

Secondary

To describe and compare the percentages of subjects in the MenACWY (3 lots combined) and Menactra vaccine groups when administered to healthy adolescents or adults (11-55 years of age) in terms of:

- Immediate hypersensitivity reactions (within 30 minutes) following vaccination
- Local and systemic reactions during the period Study Day 1 – 7
- Adverse events (AEs) reported during the period Study Day 1- 29
- Medically significant AEs reported during the period Study Day 30 - 180
- Serious adverse events (SAEs) reported from Study Day 1 – 180

6. OVERALL STUDY DESIGN

6.1 Overall Study Design and Plan – Description

6.1.1 Overall Study Design

This is a phase 3, observer-blind, multi-center, randomized, controlled study in healthy subjects 11-55 years of age.

Subjects will be included in the study if in good health as judged by physical assessment and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 3432 healthy subjects 11-55 years of age will be randomly assigned to receive a single dose of either MenACWY or Menactra. Subjects will be randomized in a 1:1:1:1 ratio to one of four groups (MenACWY lot 1, lot 2, lot 3, or Menactra). Randomization will be stratified by age such that 2100 adolescents (11-18 years of age), 400 adults (19-34 years of age) and 932 adults (35-55 years of age) will be enrolled. For all subjects in the 11 to18 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adolescents as follows. For MenACWY Groups I-III, all 500 evaluable subjects in each group (Lot 1, Lot 2, Lot 3) will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects in each group will have immunogenicity testing performed for serogroups A, W, and Y. For Menactra Group IV, from a randomly selected subset of 220 evaluable Menactra subjects, 220 will have immunogenicity testing performed for serogroups A and C, 190 for serogroup W, and 160 for serogroup Y.

For all subjects in the 19 to 55 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adults as follows. For MenACWY Groups I-III combined, a randomly selected subset of 500 evaluable subjects (from approximately 1000) will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects (from the 500) will have immunogenicity testing performed for serogroups A, W, and Y. For approximately 333 Menactra Group IV subjects in the 19 to 55 years of age group, 233 will have immunogenicity testing performed for serogroups A and C, 190 for serogroup W, and 160 for serogroup Y.

Table 1: Vaccine Group and Immunogenicity Summary

Vaccine Group	Subjects enrolled	Subjects enrolled		
		11-18 yoa*	19-34 yoa**	35-55 yoa**
I MenACWY Lot 1	2574	525	100	233
II MenACWY Lot 2		525	100	233
III MenACWY Lot 3		525	100	233
IV Menactra™	858	525	100	233

*Blood samples will be collected in all adolescents (11-18 years of age) enrolled in Groups I- IV. For all groups, immunogenicity testing will be performed in a randomly selected subset of adolescents as follows. For Groups I-III, 500 evaluable subjects in each group will have immunogenicity testing performed for serogroup C, and a randomly selected subset of 350 evaluable subjects in each group will have immunogenicity testing performed for serogroups A, W, and Y. For Group IV, 500 evaluable subjects will have immunogenicity testing performed for serogroup C, 350 for serogroup A, and 300 for serogroups W and Y.

** Blood samples will be collected in all adults (19-55 years of age) enrolled in Groups I- IV. For all subjects in the 19 to 55 years of age subgroup, immunogenicity testing will be performed in a randomly selected subset of adults as follows. For MenACWY Groups I-III combined, all subjects will have immunogenicity testing performed for serogroups A and C, and a randomly selected subset of 500 evaluable subjects will have immunogenicity testing performed for serogroups W and Y. For approximately 333 Menactra Group IV subjects in the 19 to 55 years of age group, all will have immunogenicity testing performed for serogroups A and C, and approximately 300 for serogroups W and Y.

At the enrollment visit (**Visit 1, Study Day 1**), the investigator, or a person designated by the investigator, should fully inform the subjects and subjects' parents/legal guardians, as applicable, of all pertinent aspects of the trial and obtain informed consent/assent. An initial physical assessment will be performed and relevant medical history, including the subject's last diphtheria-containing vaccine, if within the past 5 years will be obtained. If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

Subjects will receive either MenACWY or Menactra by an unblinded study vaccine administrator. The subjects will be blinded to the study vaccine given. Subjects in Groups I-III will receive a single dose of one of three lots of MenACWY administered intramuscularly (IM), and subjects enrolled in Group IV will receive a single dose of Menactra (comparator) administered IM. Following vaccination, the subjects will be monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, and local and systemic reactions.

Please refer to Table 2 for a summary of relevant medical history, safety assessments, and definitions. See Section 6.5.5 "Study Procedures and Flowchart" for greater detail.

During **Visit 1 (study day 1)**, subjects will be given a Diary Card and instructed on how to complete it for Study Days 1 – 29. In addition, they will be instructed on study procedures.

On **Study Day 3 (study days 3 - 5)**, study site personnel will contact the subject or parents/legal guardians of the subject by telephone to remind them to record reaction data,

any other medical problems, and use of concomitant medication on the Diary Card. Record any medical problems reported by the subject and/or parents/legal guardians that are of concern.

On **Study Day 29 (Visit 2, study days 29 - 43)**, all subjects will complete a medical office visit to assess their health status (See Table 1). Sites will perform a physical assessment, including measurement of oral temperature and examination of injection site. Any new adverse findings must be recorded onto the appropriate case report forms (CRFs). The Diary Card given at Visit 1 will be collected and subjects will be given a second diary card and instructed on how to complete it for Study Days 30 - 180.

On **Study Day 180 (study days 165 - 195)**, study site personnel will contact the subject or parents/legal guardians by telephone to assess their health status and review any safety information recorded on the worksheet (see Table 2). They will not be asked to return the worksheet. Information from the telephone interview call will be recorded on the appropriate CRFs.

Table 2: Summary of Relevant Medical History & Safety Assessments

Medical History: past diagnoses including all allergies, major surgeries requiring in-patient hospitalization, other significant injuries or hospitalizations, any conditions requiring prescription or chronic medication, I.e. >2 weeks in duration or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	
• **Last diphtheria containing vaccination, within the last 5 years**	
Immediate reaction: signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 min after vaccination
Temperature: oral temperature *if fever (≥38 ºC) is persisting beyond Day 7 it will be reported as an AE.*	For 7 days (Day 1 – 7)
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
Systemic reactions: chills, nausea, malaise, myalgia, arthralgia, headache, rash *If persisting beyond Day 7 will be reported as an AE*	For 7 days (Day 1 – 7)
All Adverse Events	For 7 days (Day 1 – 7)
Adverse Events: AEs necessitating a physician's visit and/or resulting in premature study withdrawal	From Day 8 to Day 29
Medically significant AE: **AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal,** with the **exclusion** of pre-planned visits, medical office visits, or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis **(Note, the excluded conditions above will NOT be collected from Day 30 to Day 180)**	From Day 30 to Day 180
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified.* *If SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 180
Medications: All prescription and non-prescription medications (with the exception of mineral and vitamin supplements)	For 7 days (Day 1 – 7)
Any prescription medication for treatment of reported AEs and chronic medical conditions	From Day 8 to Day 180
Vaccinations, if any, administered during subject's participation in the study, should be recorded in the subject's CRF	From Day 29to Day 180

Immunogenicity (All adolescents and adult subjects):

At Visit 1 (Day 1), prior to administration of study vaccine, a blood sample (20 ml) will be obtained for serologic evaluation. An additional blood sample (20 ml) will be collected at Visit 2 (Day 29).

Data Monitoring Committee

An independent, external DMC will be established to monitor safety by performing scheduled analyses. The chairperson of the DMC will conduct a review of SAEs as described in the DMC Charter. The DMC will be comprised of experienced vaccine clinicians who are not investigators in the trial and a statistician experienced in the monitoring and evaluation of safety data. Before the start of the trial, a DMC charter will be established specifying rules and guidelines for assessing safety. The DMC and its biostatistics support group will have access to study-subject treatment assignments and to the results of the scheduled safety analyses to make recommendations regarding Novartis Protocol V59P13 and study continuation. Details of all DMC procedures will be documented in the DMC Charter.

6.1.2 Planned Duration of Study

Expected subject enrollment interval: 3 months

Duration of individual subject's participation: 6 months

Total duration of study: 9 months

End of Trial: A phone call at 180 days is the last scheduled contact for follow-up.

6.1.3 Premature Discontinuation of the Study

The sponsor, or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study medication/vaccines etc.) will be returned to the sponsor or destroyed by the site, at the sponsor’s discretion.

6.1.3.1 Stopping/Pausing Rules

There are no predetermined stopping rules other than those described in section 6.1.3.

6.2 Discussion of Overall Study Design

This is a phase 3, observer-blind, multi-center, randomized, controlled study in healthy subjects 11-55 years of age.

The primary objective of this study is to assess the consistency of the immunogenicity of three manufactured lots of MenACWY when administered to healthy subjects 11-18 years of age. In addition, non-inferiority of safety and immunogenicity of MenACWY to the US-licensed meningococcal ACWY conjugate vaccine (Menactra™) will be assessed when administered to healthy subjects 11-55 years of age.

Subjects will be included in the study if in good health as judged by physical assessment and medical history and if they meet all other inclusion criteria and no exclusion criteria.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Healthy male and female individuals 11-55 years of age will be recruited from the local communities.

Individuals eligible for enrollment in this study are those:

1. who are 11-55 years of age inclusive and who, after the nature of the study has been explained:
    - have given written assent and/or for whom the parent or legal guardian has provided written informed consent (11-17 years of age)
    - have provided written informed consent (18-55 years of age)
2. who are available for all visits and telephone calls scheduled for the study;
3. who are in good health as determined by:
    - medical history
    - physical assessment
    - clinical judgment of the investigator

Informed consent/assent must be obtained for all the subjects before enrollment into the study.

6.3.2 Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling or unable to give written informed assent or consent to participate in the study;
2. who are perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N. meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
5. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) *(Exception: Receipt of OMP-containing Hib vaccines is permitted)*;

6. who had prior military service
7. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;
8. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within 28 days after vaccination *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination)*
9. who have received a live viral vaccine within 60 days prior to enrollment;
10. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (≥38°C) within 3 days prior to enrollment;
11. who have any serious acute, chronic or progressive disease such as
    j. history of cancer (excluding minor non-melanoma skin cancer)
    k. complicated diabetes mellitus
    l. advanced arteriosclerotic disease
    m. autoimmune disease
    n. HIV infection or AIDS
    o. blood dyscrasias
    p. congestive heart failure
    q. renal failure
    r. severe malnutrition

    (Note: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment);
12. who are pregnant or nursing (breastfeeding) mothers (Females will have a urine pregnancy test at entry, sensitive to 20 IU β-hCG)
13. If female of childbearing potential and sexually active with a male partner, has not used or does not plan to use acceptable birth control measures detailed in the section entitled "Females of childbearing potential" at least 30 days before study entry and continuing through 180 days after the last vaccine dose.

Females of Childbearing Potential

Non-childbearing potential is defined as menopausal for at least 1 year, and status post surgical sterilization, i.e. bilateral tubal ligation, bilateral oophorectomy, or hysterectomy. A urine pregnancy test will be performed on all female subjects on the same day as and prior to vaccination (Day 1, Visit 1).

Females of childbearing potential (i.e., not surgically sterile or at least 1 year postmenopausal) must have utilized one of the following methods of birth control for at least 30 days prior to study entry and agree to continue utilizing the same method of birth control for at least 180 days after vaccination:

- Hormonal contraceptive (such as oral, injection, transdermal patch, implant, vaginal ring);
- Barrier method (such as condom with spermicide or diaphragm with spermicide) each and every time during intercourse;
- Intrauterine device (IUD);
- Monogamous relationship with vasectomized partner

14. . who have epilepsy or any progressive neurological disease or history of Guillain Barré Syndrome;
15. who have a history of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
16. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
    - receipt of immunostimulants
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study
17. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
18. who have Down's syndrome or other known cytogenic disorders;
19. who are planning to leave the area of the study site before the end of the study period;
20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

6.3.3 Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

If a subject, or where applicable, the subject's legally acceptable representative(s), withdraws consent but does not revoke the HIPAA authorization, Novartis will have full access to the subject's medical records, including termination visit information. If a subject, or where applicable the subject's legal representative revokes only the HIPAA authorization, Novartis will have full access to all of the subject's medical records prior to the date and time of written revocation.

For any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial the site will:

- Maintain contact with the pregnant subject,
- Complete a "Pregnancy Report" CRF as soon as possible,
- Obtain pregnancy outcome information for "Pregnancy Follow-up" CRF.

All subjects will be clinically monitored after withdrawal, the cause of which will be recorded in detail on the “Study Termination” CRF, “Adverse Events” CRFs and, where appropriate, on the subject’s medical records. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section 6.5.4.

Whenever possible, the tests and evaluations listed for the termination visit will be carried out.

Withdrawn subjects will not be replaced.

6.4 Vaccines

6.4.1 Vaccines Administered

Adolescents and adults in the US will be assigned MenACWY Lot 1, MenACWY Lot 2, MenACWY Lot 3, or Menactra in a 1:1:1:1 ratio. (See Table 1, Section 6.1.1)

a) Investigational vaccine: MenACWY

The investigational Novartis Meningococcal ACWY conjugate (MenACWY) vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the Men CWY component.

One 0.5 mL dose of MenACWY will be administered by intramuscular (IM) injection in the left deltoid area.

b) Control vaccine: Menactra,

One 0.5 mL dose of Menactra will be administered by intramuscular (IM) injection in the left deltoid area.

NOTE: Because study and control vaccines have different appearances in the syringe and different reconstitution requirements vaccinations and safety assessments each will be performed by different study personnel to ensure blinding.

6.4.2 Identity of Investigational Vaccine

6.4.2.1 Vaccine Composition

Novartis MenACWY Conjugate Vaccine

After reconstitution the MenACWY vaccine will have the following composition per 0.5 mL of injectable solution (Table 3):

Table 3: MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

Menactra
Licensed meningococcal ACWY polysaccharide vaccine Menactra™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single 0.5 mL dose formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. (See Table 4)

Table 4: Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	4 µg
Serogroup C polysaccharide (PS)	4 µg
Serogroup Y polysaccharide (PS)	4 µg
Serogroup W135 polysaccharide (PS)	4 µg
Diphtheria toxoid protein total (Each PS is conjugated to diphtheria toxoid)	48 µg
Sodium phosphate	(b) (4)
Sodium chloride	(b) (4)

6.4.2.2 Vaccine Labeling, Storage and Packaging

All study vaccine supplies must be stored between 2 and 8°C (36-46°F). Do not freeze. Vaccines that have been stored differently from the sponsor's recommendations **must not** be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor. Batches of commercially available comparator vaccines must be stored separately from normal hospital/practice stocks in accordance with the instructions of the manufacturer.

The sponsor will supply the investigational and control vaccines. The investigator (or designee) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.

Novartis MenACWY vaccine is identified by a lot number. The last digit of the lot number is a letter that can differ within the same vaccine batch in case multiple packaging and/or labeling processes are performed. This has no impact on the vaccine composition or manufacturing process.

Novartis MenACWY Conjugate Vaccine will be supplied and packaged as a single dose per box. Each box will contain one vial and one pre-filled syringe. The vial will contain the lyophilized powder of the Men A component and the pre-filled syringe will contain the liquid solution of the Men CWY component.

For each study vaccine, the box label contains the vaccine identifier and the following information:

Protocol Number: Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at 2 - 8°C
For Clinical Trial use only
Expiry date:
Lot number:
Sponsor name:

The Men A vial label will include the identity of the investigational product, a 6-digit blank to be completed with the subject number following randomization, the protocol number, the expiry date, the lot number, the required storage conditions, the cautionary statement “For clinical trial use only”, and the directions for use.

The label for the pre-filled syringe containing Men CWY will include the same information as the vial label.

Menactra

Novartis will provide Menactra to the site. All study vaccine must be stored at 2°C to 8°C (36°F to 46°F) in a monitored, temperature-controlled refrigerator housed in a secure area of the study site until ready for administration by personnel. Do not freeze.

The commercial label for Menactra will remain intact. Novartis will provide a separate box with the V59P13 protocol label to include individual labels for the syringe and drug accountability log. The label will include:

Protocol Number:
Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at 2 - 8°C
For Clinical Trial use only
Expiry date:

Lot number:
Sponsor name:

6.4.2.3 Vaccine Administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in the Manual of Operations. Only unblinded personnel who are qualified to perform that function for the specific study site under applicable local laws and regulations will administer all vaccines.

Novartis MenACWY Conjugate Vaccine

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in the Manual of Operations. Only unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site will administer all vaccines.

The vaccine must be **well shaken** and visually inspected before use. The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol). Before vaccination, the skin must be dry. **DO NOT inject intravascularly**.

In the event that any of the vaccine dosing units is damaged, unusable, or has been stored or exposed to temperatures outside the permitted range, a replacement set (as appropriate to randomization) should be supplied.

Menactra Conjugate Vaccine

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the deltoid region. Before injection, the skin at the injection site should be cleaned and prepared with a skin disinfectant. After insertion of the needle, the administrator should aspirate to ensure that the needle has not entered a blood vessel.

Menactra should not be administered intravenously, subcutaneously, or intradermally.

Potential drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines or to individuals with a history of allergy to mercury-containing compounds, such as sodium ethylmercurithiosalicylate. Neither **MenACWY** nor Menactra include mercury-containing compounds.

Any oral temperature ≥ 38°C or serious active infection is reason for delaying vaccination. Immunization should also be delayed according to instructions in section 6.3.3.

Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4.3 Method of Assigning Subjects to Vaccination Groups

IVRS will be used for randomization (please refer to the V59P13 Study Manual for more information).

Subjects who meet the study admission criteria will be enrolled into the study and IVRS will assign a 6-digit subject number.The first two digits identify the study site, for example "01". The next four digits identify the subject within the site and will be assigned sequentially, for example "0001" as the first subject enrolled.

Subjects who meet the initial study inclusion and no exclusion criteria will be randomly assigned to receive either MenACWY or Menactra. Approximately 3432 healthy subjects will be randomized in a 1:1:1:1 ratio to one of four groups (MenACWY lot 1, lot 2, lot 3, or Menactra). Randomization will be stratified by center and age group such that 2100 adolescents (11-18 years of age), 400 adults (19-34 years of age) and 932 adults (35-55 years of age) will be enrolled.

Immunogenicity testing for specific serogroups will be done on a randomly selected subset of the subjects. Refer to Table 1 for the sample size selection within each treatment arm and serogroup. The subset upon which the serology assays will be performed will be based on a random selection from all the subjects performed by the third-party IVRS vendor. The IVRS vendor will send a dataset to Novartis listing the subject numbers to test for each serogroup. The random selection will be done in nested subsets. For example, in the 11-18 year old MenACWY groups, the subset of 350 subjects within each lot to be tested for serogroups A, W, and Y will be chosen from the 500 subjects selected to be tested for serogroup C in that lot. In this case, 350 subjects will be tested for four serogroups, 150 subjects will be tested only for serogroup C, and 25 subjects would not be tested at all.

6.4.4 Selection of Doses in the Study

The doses used in this study are based upon dose and formulation finding studies conducted in toddlers in Finland, Germany and the United States. In one trial (Finland and Germany), more than 500 toddlers received at least one dose of one of 5 formulations of MenACWY (approximately 100 subjects per group). While all formulations were well tolerated and immunogenic, the formulation used in this trial appeared to provide optimal responses for Serogroup A relative to all other formulations.

In another trial conducted in the US, 235 toddlers received one dose of three formulations of investigational MenACWY conjugate vaccine; two formulations without adjuvant at a fixed dose of 5 µg or 10 µg per oligosaccharide antigen and one formulation of 5 µg per oligosaccharide adjuvant with aluminum phosphate adjuvant. Although preliminary data suggested improved immunogenicity (as measured by GMTs) for at least one vaccine antigen component (W) in the presence of adjuvant, there was no apparent difference in the responses to the other antigens (A, C and Y). A subsequent toddlers study (V59P7) supported the conclusion that addition of the adjuvant provided no meaningful improvement in immunogenicity. For additional information, please see the Investigator Brochure.

6.4.5 Blinding

The trial is designed as an observer-blind study. During the study, designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines neither to the subject nor to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, except in an emergency. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. If the study vaccine code is supplied to the investigator in the event of an emergency, the investigator must notify the study monitor immediately. The date and time, along with the reason for the unblinding, should be noted. Study vaccine codes will not be freely available to the investigator or personnel monitoring the trial until after the completion of the trial and final data review. Sponsor and subjects will be blinded to treatment. An IVRS vendor external to the sponsor (who will perform the randomization) and individuals involved in drug packaging will be unblinded. Members of the DMC will also be unblinded.

6.4.6 Prior and Concomitant Therapy

All prescription medication and antibiotics, including non-study vaccines, being taken by the subjects on entry to the study and all prescription medication and antibiotics given in addition to the study vaccine during this clinical trial are to be regarded as concomitant medication and must be documented on the “Concomitant Medications” CRF. If therapy was started prior to the beginning of the study, the box titled “prestudy” under the “start date” field on the “Concomitant Medications” CRF should be checked.

CONCOMITANT VACCINES:

No concomitant vaccines will be administered during Visit 1.

The following vaccines are allowed if given at least 29 days after study vaccination and after the Visit 2 blood draw:

- Normal routine or catch-up vaccinations appropriate for this age group
- Recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination).*

Vaccinations will be reported as concomitant medications on the subject's CRF.

6.4.7 Vaccination Compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator or designee will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be returned to the sponsor or destroyed at the investigational site according to the relevant Novartis SOP. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.4.8 Adherence to Randomization

Adherence to randomization will be verified by a designated and unblinded Study Monitor independent of the staff involved in the regular monitoring of the study by checking the randomization list against the vaccination records maintained at the study site.

An unblinded, appropriately qualified person, will prepare/administer the vaccine as indicated by IVRS for the individual subject. The investigator or designate administering the vaccine as well as the Study Monitor will not be unblinded during the conduct of the study.

6.5 Immunogenicity and Safety Variables

6.5.1 Immunogenicity and Safety Measurements Assessed

The Time and Events Table (Table 7) in the Synopsis and section 6.5.5 describe the required evaluations.

6.5.2 Appropriateness of Measurements

The measures of safety used in this study are routine clinical procedures. Selected local and systemic reactions are routinely monitored in vaccine clinical trials as indicators of reactogenicity. They will be closely followed and stringently reported.

6.5.3 Immunogenicity Variables

The ability of MenACWY vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Activity, hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed.

6.5.4 Safety Variables

A brief medical history will be obtained and physical assessment performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.1.1 and 6.5.5.

6.5.4.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, the study site investigator and Novartis Vaccines and Diagnostic, Inc.'s Medical Monitor will make a clinical assessment as to whether continued follow-up of the AE is warranted.

The investigator will determine the severity of events reported on the "Adverse Events" CRF using the following definitions:

Mild:	no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The investigator will determine the relationship of the study treatment to an AE based on the following definitions:

<u>Not Related</u>

The AE is not related if exposure to the investigational vaccine has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

<u>Possibly Related</u>

The administration of the investigational vaccine and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The investigator will determine the relationship of the study treatment to an AE.

6.5.4.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization, but based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Of note: a "possible vaccine failure" should be reported as a serious AE only if it resulted in an infectious disease, which should have been prevented by the vaccine implied.

Adverse events that do not fall into these categories are defined as **non-serious**.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history CRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the

hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

6.5.4.3 Local and Systemic Reactions

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post vaccination, will be recorded on the "Local and Systemic Reactions" rather than the "Adverse Events" CRF.

The assessment of local reactions will include: injection site pain, erythema, induration

The assessment of systemic reactions will include: chills, nausea, malaise, myalgia, arthralgia, headache, and rash.

The assessment of other indicators of reactogenicity will include: oral temperature (≥ 38°C), stayed home due to reaction, and use of analgesics/antipyretics

6.5.4.4 Clinical Laboratory Tests

Clinical laboratory tests will not be required by the protocol. Investigators are instructed to report abnormal laboratory test results if any are observed in the course of routine medical care. Abnormalities in clinical laboratory tests that are considered clinically significant by the investigators will be recorded on the "Adverse Events" CRF.

6.5.4.5 Documentation/Monitoring/Reporting of Safety Variables

All study subjects will be observed for at least 30 minutes after vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena (such as rashes, itching, or other allergic manifestations). Each subject, or where applicable, the subjects' legally acceptable representative(s) will be instructed to complete a diary card for 7 days following study vaccine administration, to describe local reactions, systemic reactions, and other selected indicators of reactogenicity. If a local and systemic reaction ends on day 7, it will be recorded on the "Local & Systemic Reactions" CRF. If it continues beyond 7 days after vaccination, it will be recorded on the "Adverse Events" CRF. All medically significant adverse events (Refer to Section 6.1.1 Table 2) must be reported and documented. The period of observation for adverse events extends from the time the subject gives informed consent/assent until he or she undergoes the final study examination. Any medical event that occurs after the Informed Consent Form is signed, but prior to receiving study vaccine and is related to a study procedure, will be documented as an adverse event and recorded on the AE CRF. Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the Medical History CRF. The investigator will monitor all AEs, regardless of severity, until resolution. All subjects experiencing adverse events - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an "Adverse Events" CRF and on

the "Vaccine Serious Adverse Event" form, if necessary, which is part of the investigator's study file. All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

In addition, any event resulting in a subject's withdrawal from study should be reported according to section 6.3.3 "Removal of Subjects from Therapy or Assessment". All SAEs which occur during the course of the trial, whether considered to be associated with the study vaccination or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor: Jina Shah MD
Phone number: +1 (510) 923-5509
Fax number: +1 (510) 923-3450

Study Monitor: Tanja Odzak MS
Phone number: +1 (510) 923-3449
Fax number: +1 (510) 923-3450

For trial related **emergencies out of office hours** please contact: 1 (510) 502-3650

As far as possible, all points raised on the "Vaccine Serious Adverse Event" form need to be addressed and faxed immediately to the Medical Monitor or Study Monitor. The investigator must retain the original form. The event must also be documented on the "Adverse Events" CRF. After receipt of the initial report, the Medical Monitor/Study Monitor will review the information and contact the investigator if it is necessary to obtain further information for assessment of the event. Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF(s) in addition to the outcome of the AE. Any serious adverse reaction must be reported to the IRB in a timely manner. Adequate documentation will be provided to the sponsor showing that the IRB has been properly notified. The sponsor must also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious and non-serious adverse drug reactions to the regulatory authorities and the IRB.

If required, a follow-up report including all new information obtained on the serious adverse event must be prepared and sent to the Medical Monitor/Study Monitor. The report should be marked "Follow-up report".

The investigator will submit, per institutional requirement, copies of all these reports to the IRB and other relevant authorities.

Post-Study Events

Any AE occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine - and therefore a possible adverse drug reaction - must be reported.

6.5.5 Study Procedures and Flowchart

Informed consent/assent must be obtained from the subject, or where applicable, the subject 's legally acceptable representative(s) prior to the performance of any trial specific tests or evaluations, i.e., any unusual or non-routine procedures that involve risk, however trivial, to the subject.

Study Day 1: Screening/Baseline and Vaccination

Subjects should be screened prior to vaccination at Visit 1 to ensure they meet all inclusion and no exclusion requirements. If the investigator determines the subject is not eligible, s/he should document the reason for exclusion.

a) Fully inform the subjects and subjects' parent/legal guardian, as applicable (hereafter referred to collectively as "subjects" for clarity) of all pertinent aspects of the trial and obtain informed consent/assent prior to the performance of any trial specific tests or evaluations, i.e. any unusual or non-routine procedures that involve risk, however trivial to the subject.

b) Obtain and record relevant medical history

c) Investigator or designee performs initial physical assessment including measurement of oral temperature, weight and height, and a check of general appearance and systems evaluation. A urine pregnancy test will be conducted for all females

d) If the subjects are in good health according to the clinical judgment of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

e) Obtain blood sample via venipuncture (20 mL) from all subjects.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

f) Unblinded site personnel will administer the study vaccine. Subjects will receive either MenACWY or Menactra.

g) Observe subject in the clinic for 30 minutes.

h) Examine the injection site of the vaccine for local reactions at the end of the 30-minute observation period.

i) Instruct subjects in the evaluation of local and systemic reactions, and recording of oral temperature.

j) Dispense diary cards and instruct subject on how to complete Diary Card for the study Days 1 – 29.

Study Day 3 (study days 3 - 5)

a) Study site personnel will contact the subject or parent/legal guardian of the subject by telephone. The purpose of this contact is the following:

- Remind the subject or parent/legal guardian to record reaction data, any other medical problems, and use of concomitant medication on the Diary Card.

- Record any medical problems reported by the subject and/or parent/legal guardian that is of concern.

Study Day 29, (study days 29 - 43)

All subjects will complete a medical office visit to assess their health status. See Table 2

a) Perform a physical assessment, including measurement of oral temperature and examination of previous injection site. Any new adverse findings must be recorded onto the appropriate CRFs.

b) Collect and review diary card for Study Days 1 - 29 with subject and/or parent/legal guardian. For Study Days 1 – 7, collect and record information regarding all local and systemic reactions and all AEs. For Study Day 8 through Visit 2, collect and record information regarding SAEs, events requiring a medical office visit, or any event resulting in a subject's early termination reported. Record information obtained on the appropriate CRFs.

c) Collect prescription medications used to treat reported adverse events. Record information obtained on the appropriate CRFs.

d) Obtain blood sample via venipuncture (20 mL). Process blood and store serum for serologic evaluation.

e) Dispense worksheet and give subject or parent/legal guardian instructions for its completion.

f) Remind subject and parent/legal guardian that they will be contacted in 5 months.

Study Day 180 (study days 165 - 195),

Contact the subject or parent/legal guardian of the subject by telephone to assess their health status and review any safety information recorded on the worksheet. Subjects will not be asked to return the worksheets. Information from the telephone interview will be recorded on subjects' CRFs.

Table 7: TIME AND EVENTS

Visit Number	**1**	☎	**2**	☎
Study Day (window)	Day 1	Day 3 (Study days 3 – 5)	Day 29 (Study days 29 to 43)	Day 180 (Study days 165 – 195)
Obtain Informed consent/assent	X			
Medical History	X			
Physical Assessment [a]	X		X	
Obtain Blood Sample	X		X	
Administer Study Vaccine [b]	X			
Injection-site Examination	X [b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications [c, d]	X		X	X
Serious Adverse Events [e]	X	X	X	X
Study Termination				X

Note: Day 1 is defined as day of study vaccination.

[a] The physical assessments at visit 1 (study day 1) should be performed by a study physician or designee.
[b] All subjects will be observed in the clinic for 30 minutes after vaccination.
[c] Collect data on concomitant medications prescription and non prescription through the first 7 days.
[d] Collect data on concomitant medications (prescriptions only) from Day 8 through Day 180.
[e] Collect information regarding any SAE or any event resulting in a subject's early termination any time during the subject's study participation. A 6-month follow up call will be made to assess the occurrence of SAEs and significant medical events (Please see definitions on TABLE 2, Section 6.1 1).

6.5.5.1 Study Evaluations

Blood samples taken in the following time windows will be evaluable:

Pre-immunization: day 1

Post-immunization: day 29 (window: + 14 days)

6.5.5.1.1 Laboratory Assessments

Not applicable.

6.5.5.1.2 Labeling and Storage of Serum Samples for Serology

Twenty (20) mL of whole blood should be available to be processed for serum for use in assays.

The blood will be centrifuged on the same day and the serum will be distributed in four equal aliquots using the tubes provided. The aliquots will be stored at a temperature of minus 18°C or below.

Each serum tube will be labeled with an identifying bar code including subject number, and protocol number. Serum samples will be sent to the sponsor or will be collected by a representative of the sponsor.

For further information see Appendix B.

Complete instructions for labeling and storage of serum samples are included in the Study Reference Manual.

6.6 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained at the latest during the initiation visit. During each monitoring visit qualified staff representing the sponsor will perform source data verification. A CRF collation supplied by the sponsor will be completed for each subject. Trained delegates of the sponsor will check the entries.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor's Clinical Quality Assurance (CQA) department will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms, the Analysis Plan and the Subject Information and Consent Form.

6.6.1 Study Monitoring

The clinical study site will be monitored by regular site visits and telephone calls to the investigator by qualified staff representing the sponsor following Novartis Vaccines' internal SOP and/or those procedures that are specified by Novartis Vaccines for monitoring trials. The details for monitoring this study (including the expected average monitoring frequency and when the first monitoring visit will be performed) will be defined in the monitoring plan. By frequent communication, the site monitor will ensure that the study is conducted according to the protocol.

CRFs and all original data collected at the site including subjects' medical records should be available for review during monitoring visits. During these visits, the site monitor should review drug accountability records and document retention including the Investigator's Study File. Additionally, the site monitor should check that clinical study procedures are observed and discuss any problems with the investigator.

6.6.2 Source Data Verification and Audits

Inspection and examination of CRFs and source documents (all original recordings, laboratory reports, medical records) - giving due consideration to data protection and medical confidentiality - will be undertaken by representatives of the sponsor. All data not recorded directly on the CRFs as defined in section 6.10 of this study protocol must be verified by checking CRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol. Source data verification will be performed and recorded following Novartis internal SOP. The subject or the subject's legally acceptable representative must also allow access to the subject's medical records. Each subject, or the subject's legally acceptable representative, will be informed of this prior to the start of the study.

During or after the clinical study, the regulatory authorities, the IRB and/or representatives of the sponsor may request access to all source documents, CRFs and other study documentation for on-site audit or inspection.

6.7 Data Management

All CRF data (except for comments fields on the "Medical History" and "Comments" CRFs and the "Other, specify" item on the "Screen Log", if applicable), will be entered in duplicate into a (b) (4) database by BCDM, Novartis.

Data validation will be performed using the programming languages (b) (4) (b) (4) Data quality assurance will be performed by doing a 100% check of all database updates resulting from the resolution of queries, and by estimating the database error rate with 95% upper confidence limit. The latter must be below the departmental accepted level of 0.5%. Analysis will be performed by BCDM using (b) (4) version (b) (4) according to a predefined Analysis Plan (AP), developed by the study Biostatistician.

All serology data analyzed by Clinical Serology Marburg, Novartis Vaccines will be entered into the (b) (4) database by Clinical Serology Marburg, Novartis Vaccines. All results will be checked in the laboratory for validity and completeness by three persons before access to the data is granted to BCDM, Novartis.

6.7.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

6.7.2 Data Protection

Novartis respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

6.8 Changes in the Conduct of the Study or Planned Analysis

Planned changes in the conduct of the study will be described in protocol amendments; changes in the planned analysis will be described in the clinical study report.

An amendment is a written description of change(s) to or formal clarification of a study protocol.

The IRB must be informed of all amendments and if necessary prior review and documented approval/favorable opinion must be sought for ethical aspects. Approval must also be obtained from the authorities, if necessary.

The sponsor, the investigator, the IRB, and authorities, if necessary, will agree upon such amendment prior to implementation.

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical Plans

The statistical evaluation of the results will be performed by BCDM as predefined in the AP. The statistical tables and graphs will be generated using (b) (4) version (b) (4)

Baseline is defined as the time of first vaccination.

Definition of populations to be analyzed:

a. Enrolled population: all subjects who have signed an informed consent, undergone screening procedures, and have been randomized.

b. Exposed population: all enrolled subjects who actually receive a study vaccination

c. Safety population: all subjects in the exposed population who provide post-baseline safety data

d. Intention-to-treat (ITT) population, Immunogenicity: all subjects in the enrolled population who
   - receive a study vaccination, and
   - provide at least one evaluable serum sample before or after baseline

e. Modified Intention-to-treat (MITT) population, Immunogenicity: all subjects in the ITT population who
   - receive a study vaccination, and
   - provide at least one evaluable serum sample before and after baseline

f. Per protocol (PP) population, Immunogenicity: all subjects in the MITT population who:
   - receive the vaccine correctly, and
   - provide evaluable serum samples at the relevant time points, usually paired, and
   - have no major protocol deviation as defined prior to unblinding

   A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

6.9.1.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment will be calculated overall and by vaccine group and for each age group (i.e.11-18, 19-34, 35-55 yoa)

Distributions of subjects by sex and ethnic origin previous vaccination will be summarized overall and by vaccine group and for each age group.

6.9.1.2 Analysis of Immunogenicity Criteria

Primary

- To demonstrate lot-to-lot consistency of three lots of MenACWY as measured by hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination

  Criteria for assessing objective: for all serogroups and for all pairs of lots, the two-sided 95% confidence interval (CI) for the ratio of hSBA GMTs at one month after the vaccination is contained within the [0.5; 2.0] interval.

- In the 11 to 18 yoa adolescent group, to compare the immunogenicity response one month after a single vaccination of MenACWY to that of Menactra as measured by percentage of subjects with seroresponse.

- In the 19 to 55 yoa adult group, to compare the immunogenicity response one month after a single vaccination of MenACWY to that of Menactra as measured by percentage of subjects with seroresponse.

  Criteria for assessing objective: for any of the four serogroups, the lower limit of the two-sided 95% confidence interval (CI) around the difference (MenACWY – Menactra) in the percentage of subjects with seroresponse is greater than –10%.

The primary immunogenicity endpoint for assessing non-inferiority is the percentage of subjects with seroresponse for N. meningitidis serogroups A, C, Y and W-135 one month after vaccination.

Seroresponse for a subject is defined based on the subject's pre-immunization titer. For a subject with a pre-immunization titer greater than or equal to 1:4, e.g., 1:x, seroresponse is achieved if the subject's post-immunization titer is 1:4x or greater. For a subject with a

pre-immunization titer less than 1:4, a seroresponse is achieved if the subject's post-immunization titer is 1:8 or greater.

The null hypothesis associated with the non-inferiority immunogenicity objective in the 11 to 18 yoa adolescent group is that for at least one serogroup, the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (e.g., MenACWY {pooling of Groups I, II, III} *minus* Menactra {Group IV}) is ≤ -10%. The null hypothesis for the 19 to 55 yoa adult group is similar.

The 95% CIs for each serogroup for the difference in proportions (MenACWY - Menactra) will be constructed. If the CI is entirely to the right of -10%, then non-inferiority will be declared for that serogroup. Moreover, if the CI is entirely to the right of 0%, then the MenACWY serogroup will be considered to have a statistically significant higher immune response compared to that same serogroup of Menactra.

The hSBA GMTs at baseline (Day 1), one month after the vaccination (Day 29) in response to *N. meningitidis* serogroup A, C, W and Y will be calculated. GMT increase (geometric mean ratio, [GMR]) at Day 29 as compared to baseline values (Day 1) will also be calculated. The GMTs, GMRs, 2-sided 95% CIs, and median, minimum and maximum values will be calculated for each vaccine group and for each age group within each serogroup.

The GMTs, GMRs and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) titers and their 95% CIs obtained from an Analysis of Variance (ANOVA) model with vaccination group and center as factors in the model. Statistical details for the use of this method and possibly others (e.g., Analysis of Covariance) will be provided in the (statistical) analysis plan. If for all serogroups and for all pairs of vaccine lots the two-sided 95% CI of the GMT ratio is within [0.5; 2.0] then lot-to-lot consistency will be demonstrated.

Secondary

– To compare immunogenicity response one month after one vaccination of MenACWY to immunogenicity of Menactra as measured by percentage of subjects with hSBA≥1:8 (or hSBA≥1:4).

  Criteria for assessing objective: for any of the four serogroups, the lower limit of the two-sided 95% confidence interval (CI) around the difference (MenACWY *minus* Menactra™) of the percentage of subjects with hSBA≥1:8 (or hSBA≥1:4) is greater than -10%.

The 95% CIs for the difference in proportions (given serogroup for MenACWY - given serogroup for Menomune) will be constructed. If the CI is entirely to the right of -10%, then non-inferiority will be declared for that serogroup. Moreover, if the CI is entirely to the right of 0%, then the immunogenicity of MenACWY for that serogroup will be considered statistically significant higher compared to Menactra vaccine.

– To compare immunogenicity response one month after one vaccination of MenACWY to immunogenicity of Menactra as measured by hSBA GMTs.

  Criteria for assessing objective: for any of the four serogroups, the lower limit of the two-sided 95% confidence interval (CI) around the ratio of hSBA GMTs between MenACWY and Menactra, one month after vaccination, is above 0.5.

6.9.1.3 Analysis of Safety Criteria

Primary

The primary safety analysis is the comparison of the percentage of subjects presenting at least one severe systemic reaction to the MenACWY vaccine with the percentage of subjects presenting at least one severe systemic reaction to the Menactra vaccine during the first 7 days (Day 1-7) following a single dose administered to healthy subjects 11-55 years of age.

The null hypothesis associated with the safety objective is that the upper limit of the two-sided 95% confidence interval for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra groups ($p_{MenACWY} - p_{Menactra}$) is ≥6%.

MenACWY conjugate vaccine will be considered non-inferior to Menactra vaccine with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference (MenACWY vaccine group minus Menactra vaccine group) of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1-7) after vaccination is <6%.

Secondary

Local and Systemic Reactions

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

For the local and systemic reaction safety variables, differences among the vaccine groups after each scheduled immunization and after any immunization with respect to all variables (including fever) will be analyzed by using Pearson's chi-square test, or Fisher's Exact test where appropriate.

Other Adverse Events

From a perspective of detecting uncommon local or systemic reactions, or AEs, Table 6.9.1.3-1 below gives the probabilities of observing at least one subject with one such event for either vaccine group for several underlying event rates.

Table 6.9.1.3-1: Probability of Observing at Least One Subject with an Uncommon Event in the MenACWY and Menactra groups (11-55 yoa) for Given Underlying Event Rates

Underlying Event Rate	Probability of observing at least one event in Group I, II, or III (MenACWY) N=2574	Probability of observing at least one event in Group IV (Menactra) N=858
1/100	>0.99	>0.99
1/200	>0.99	0.99
1/500	0.99	0.82
1/1000	0.92	0.58

All the adverse events occurring during the study, judged either as related to vaccination or not by the investigator, will be recorded as specified in Section 6.1.1.

The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by age group (i.e. 11-18, 19-34, 35-55 yoa). When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

6.9.1.4 Interim Analysis Planned

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled "Interim Analysis in a Clinical Trial".

After all subjects have completed Visit 2, (one month after vaccination), a group unblinded analysis may be performed to assess immunogenicity.

In addition, a preliminary analysis may be performed to assess safety after all subjects have completed Visit 2 (one month after vaccination, including local and systemic reactions and body temperature within 7 days of immunization and SAEs).

The results of these analyses will not alter the course of the trial.

6.9.1.5 Preliminary Analysis

6.9.2 Determination of Sample Size

Immunogenicity

Primary Lot-to-Lot Consistency

The within group standard deviation for the log10 hSBA titers was assumed equal to 0.73 for serogroup A, 1.06 for serogroup C, 0.65 for serogroup W, and 0.80 for serogroup Y. These estimates were obtained, respectively, as the square root of the upper limit of the 80% CI of the within group variance observed for each serogroup in the previous Novartis MenACWY V59P6 study. The power to reject the null hypothesis associated with the primary immunogenicity objective is the probability that, for each serogroup, for all three pairs of MenACWY vaccine lots simultaneously, the two-sided 95%confidence interval (CI) for the ratio of GMTs at 1 month after vaccination is entirely contained within the interval [0.50, 2.00]. For each serogroup, using the standard deviations given above, the power (and also sample sizes) was approximated by performing 5000 simulations for underlying GMT ratios (r) ranging from 1.0 to 1.6. (See Tables 6.9.2-1 and 6.9.2-2 below). In each replication, three independent samples were drawn from normal distributions with means log10(r), {log10(r)}/2, and 0, respectively, with the common standard deviation for that serogroup. For example, the simulated power for each serogroup to rule out a 2-fold difference was computed as the percentage of replications in which, for all three pairs of vaccine lots simultaneously, the 95% CI was contained within the interval [0.5, 2.0].

Table 6.9.2-1: Sample Size Per Group (Obtained by Simulation) to Achieve 80% or 90% Power for 95% CIs of the Ratio of GMTs from All Three Lots to be Contained Within [0.5, 2.0] by Serogroup and Underlying GMT Ratio

Serogroup	Highest:Lowest GMT Ratio	N Per Group for 80% Power	N per Group for 90% Power
A	1.0	160	190
	1.2	200	250
	1.4	360	470
	1.6	900	1200
C	1.0	340	400
	1.2	420	530
	1.4	750	1000
	1.6	1900	2500
W	1.0	130	150
	1.2	160	200
	1.4	280	370
	1.6	710	950
Y	1.0	200	230
	1.2	240	300
	1.4	440	550
	1.6	1100	1400

From Table 6.9.2-1 above, the sample size to achieve 90% power is much higher for serogroup C than for A, W, and Y. In order to ensure high power for serogroup C, 525 subjects will be randomized to each of the 3 MenACWY lots to obtain 500 evaluable subjects. In order to maintain the 1:1:1:1 treatment group balance in the randomization, 525 Menactra subjects will also be enrolled. In addition, in order to conserve human complement donor resources for A, W, and Y, it was decided to assay a smaller number of evaluable subjects for each of these serogroups. Table 6.9.2-2 below shows the power for various sample sizes per group by serogroup and underlying GMT ratios, and overall power for the 95% CIs of the ratio of GMTs from all three pairs of lots to be contained within [0.5, 2.0].

Table 6.9.2-2: Power (Obtained by Simulation*) for Various Sample Sizes Per Group by Serogroup and Underlying GMT Ratios, and Overall power for the 95% CIs of the Ratio of GMTs from All Three Lots to be Contained within [0.5, 2.0]

		Power for Each Serogroup Using Simulation of Three Tests				
Sample Size Per Group	Highest:Lowest GMT Ratio	A	C	W	Y	Overall Power
250	1.0	0.9740	0.5568	0.9958	0.9296	0.5020
	1.2	0.8928	0.4366	0.9592	0.8090	0.3025
	1.4	0.6232	0.2512	0.7402	0.5270	0.0611
	1.6	0.3016	0.1140	0.3822	0.2468	0.0032
300	1.0	0.9942	0.7170	0.9992	0.9784	0.6969
	1.2	0.9476	0.5684	0.9852	0.8896	0.4721
	1.4	0.7156	0.3410	0.8136	0.6276	0.1246
	1.6	0.3524	0.1478	0.4438	0.2926	0.0068
350	1.0	0.9986	0.8226	0.9999	0.9916	0.8145
	1.2	0.9736	0.6854	0.9932	0.9440	0.6257
	1.4	0.7880	0.4076	0.8740	0.6952	0.1952
	1.6	0.4044	0.1774	0.4990	0.3330	0.0119
400	1.0	0.9992	0.8912	0.9999	0.9978	0.8884
	1.2	0.9892	0.7748	0.9978	0.9678	0.7401
	1.4	0.8504	0.4810	0.9212	0.7782	0.2932
	1.6	0.4624	0.2170	0.5548	0.3898	0.0217
450	1.0	0.9998	0.9430	0.9999	0.9990	0.9418
	1.2	0.9968	0.8256	0.9996	0.9866	0.8116
	1.4	0.8856	0.5342	0.9428	0.8248	0.3679
	1.6	0.5062	0.2446	0.6048	0.4286	0.0321
500	1.0	0.9999	0.9694	0.9999	0.9998	0.9690
	1.2	0.9976	0.8742	0.9994	0.9916	0.8643
	1.4	0.9180	0.5978	0.9658	0.8596	0.4556
	1.6	0.5520	0.2782	0.6502	0.4784	0.0478

* Uses simulation to calculate the power of the three tests for equivalence (lot 1 vs. lot 2, lot 1 vs. lot 3, lot 2 vs. lot 3) for each serogroup, and then multiplies the results over the four serogroups for the overall power.

With 500 evaluable subjects per lot assayed for serogroup C, and 350 evaluable subjects per lot assayed for serogroups A, W, and Y, the power to reject the null hypothesis associated with the primary lot-to-lot immunogenicity objective and demonstrate immunologic consistency for each serogroup is 97%, >99%, >99%, >99% for C, A, W,

and Y, respectively. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic consistency is equal to 96%.

Primary Seroresponse

The estimate of the percentage of subjects with seroresponse for each serogroup as observed in the previous Novartis MenACWY V59P6 study in adolescents 11-17 yoa is shown in Table 6.9.2-3 below.

Table 6.9.2-3: Percentage of subjects for each serogroup with Seroresponse as observed in Novartis study V59P6

	Seroresponse	
Serogroup	**MenACWY N=147-148**	**Menomune N=152-158**
A	81%	41%
C	75%	54%
W	85%	71%
Y	86%	66%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in Rabbit Complement SBA (rSBA) and in terms of GMTs.

Given the results in Table 6.9.2-3 we can assume that, for each serogroup, the percentage of subjects with seroresponse is 0%, 5%, or 10% higher in the MenACWY group compared to Menactra. Table 6.9.2-4 below shows, for each serogroup, the number of subjects that will be tested by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 6.9.2-4: Number of subjects to be tested by hSBA for 90% power to demonstrate non-inferiority for serogroups A,C,W and Y, given estimated percent of subjects with Seroresponse in MenACWY and Menactra groups

Serogroup	Percent of subjects with Seroresponse MenACWY group (pooling of Groups I, II, III)	Percent of subjects with Seroresponse Menactra group (Group IV)	Number of subjects evaluated in each group in order to have 90% power
A	76%	76%	384
	81%	76%	158
	86%	76%	80
C	70%	70%	442
	75%	70%	186
	80%	70%	98
W	80%	80%	337
	85%	80%	135
	90%	80%	66
Y	81%	81%	324
	86%	81%	129
	91%	81%	62

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%

Table 6.9.2-5 below shows sample sizes in the Menactra group to demonstrate non-inferiority with approximate 99% power for serogroups A, C, W, Y given estimated percentages of subjects with seroresponse in the MenACWY and Menactra groups. In the MenACWY group there will be 1500 subjects with results for serogroup C, and 1050 subjects with results for serogroups A, W, and Y.

Table 6.9.2-5: Sample Sizes in the Menactra Group to Demonstrate Non-Inferiority with Approximately 99% Power for Serogroups A, C, W, Y Given Estimated Percentage of Subjects with Seroresponse in MenACWY and Menactra Groups

	MenACWY Group (Groups I, II, III Pooled)		Menactra Group (Group IV)		
Serogroup	**Percentage with Seroresponse**	**N / Group**	**Percentage with Seroresponse**	**N / Group**	**Power for Non-Inferiority**
A	76%	1050	76%	500	99%
	81%	1050	81%	350	99%
	81%	1050	76%	220	99%
	86%	1050	76%	110	99%
C	70%	1500	70%	500	99%
	75%	1500	75%	500	99%
	75%	1500	70%	220	99%
	80%	1500	70%	120	99%
W	80%	1050	80%	500	99%
	85%	1050	85%	300	99%
	85%	1050	80%	190	99%
	90%	1050	80%	100	99%
Y	81%	1050	81%	470	99%
	86%	1050	86%	300	99%
	86%	1050	81%	160	99%
	91%	1050	81%	85	99%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

To be conservative, we can assume that, for each serogroup, the percentage of subjects in the 11 to 18 yoa adolescent group with seroresponse is similar in the MenACWY group compared to Menactra. From Table 6.9.2-5 above, with 1500 evaluable subjects assayed for MenACWY serogroup C, 1050 evaluable subjects assayed for MenACWY serogroups A, W, and Y, 350 evaluable subjects assayed for Menactra serogroup A, 500 evaluable subjects assayed for Menactra serogroup C, and 300 subjects assayed for Menactra serogroups W and Y, the power to reject the null hypothesis associated with the non-inferiority immunogenicity primary objective and demonstrate non-inferiority for each serogroup is 99% for each of the serogroups A, C, W, and Y. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority is equal to 96%.

Applying the same assumptions used for the 11 to 18 yoa adolescent group to the 19 to 55 yoa adult group, the overall power to demonstrate immunologic non-inferiority in the 19

to 55 yoa age adult group is estimated to be 90%. The estimate of the overall power across the three primary objectives is 83% (=96% X 96% X 90%).

Secondary

Table 6.9.2-6 below shows the power to demonstrate, simultaneously, for a given serogroup that for each of the 3 pairs of lots the 95% confidence intervals for the difference in percentage responders between the lots is within (-10%, 10%).

Table 6.9.2-6: Power to Demonstrate that for Each Pair of Lots the 95% C.I. for the Difference in Percentage of Responders (hSBA ≥ 1:8) Between the Lots is within (-10% , 10%) for Underlying Event Rates of 70% to 90%

Underlying Event Rate (hSBA ≥ 1:8)	Simulated Power for Three Lots with		
	N=350 per Lot	N=400 per Lot	N=500 per Lot
70%	39%	52%	71%
75%	49%	61%	80%
80%	63%	75%	89%
85%	81%	89%	97%
90%	96%	98%	>99%

The estimate of the percentage of subjects with hSBA ≥1:8 for each serogroup as observed in the previous Novartis MenACWY V59P6 study in adolescents 11-17 yoa is shown in Table 6.9.2-7 below.

Table 6.9.2-7: Percentage of subjects with hSBA ≥1:8 for each serogroup as observed in Novartis V59P6 study

	% hSBA≥1:8	
Serogroup	MenACWY N=147-148	Menomune N=152-158
A	81%	41%
C	83%	62%
W	90%	84%
Y	95%	82%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in rSBA and in terms of GMTs.

Given the results in Table 6.9.2-7 we can assume that the percentage of subjects with hSBA≥1:8 is 0%, 5%, or 10% higher in the MenACWY group compared to Menactra for serogroup A and C, and is 0%. 2%, or 4% higher in the MenACWY group compared to Menactra for serogroup W and Y. Table 6.9.2-8 below shows the number of subjects to be evaluated by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 6.9.2-8: Number of subjects to be tested by hSBA for 90% power to demonstrate non-inferiority for serogroups A,C,W and Y, given estimated percent of subjects with hSBA≥1:8 in hSBA in MenACWY and Menactra groups

Serogroup	Percent of subjects with hSBA≥1:8 MenACWY group (pooling of Groups I, II, III)	Percent of subjects with hSBA≥1:8 Menactra group (Group IV)	Number of subjects evaluated in each group in order to have 90% power
A	76%%	76%	384
	81%	76%	158
	86%	76%	80
C	78%	78%	361
	83%	78%	147
	88%	78%	73
W	90%	90%	190
	92%	90%	120
	94%	90%	79
Y	93%	93%	137
	95%	93%	83
	97%	93%	51

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%.

Employing the serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs), immunogenicity of the MenACWY group will be considered non-inferior to the immunogenicity of the Menactra group if the lower limit of the two-sided 95% confidence interval of the ratio of the MenACWY to Menactra GMTs, as measured by hSBA, is ≥0.5 at one month after vaccination, when administered to healthy subjects 11 to 55 years of age. The same within group standard deviations as used for the lot-to-lot comparisons are assumed here.

Table 6.9.2-9 below shows the power to demonstrate non-inferiority for this secondary objective for each serogroup using the standard deviations for each serogroup, highest:lowest GMT ratio, and sample sizes determined above for testing the primary null hypotheses.

Table 6.9.2-9: Power Calculations for Showing Non-Inferiority of MenACWY to Menactra Using the Lower Limit of the Two-Sided 95% CI on the ratio of the MenACWY to Menactra hSBA GMTs for Each Serogroup

Serogroup	Highest:Lowest GMT Ratio	MenACWY N Per Group	Menactra N Per Group	Power for Non-Inferiority
A	1.0	1400	450	99%
	1.2	1400	450	99%
C	1.0	2000	450	99%
	1.2	2000	450	98%
W	1.0	1400	380	99%
	1.2	1400	380	99%
Y	1.0	1400	320	99%
	1.2	1400	320	99%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

With the large number of evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity secondary objective for hSBA GMTs and demonstrate non-inferiority is greater than 99% for all serogroups, assuming a true underlying highest: lowest GMT ratio of 1.

Safety

The primary safety null hypothesis is that the upper limit of the two-sided 95% confidence interval for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra ($p_{MenACWY} - p_{Menactra}$) is ≥6%. Assuming a sample size of 2574 subjects (11-55 years of age) in the MenACWY group (pooling of Groups I, II, III) and 858 subjects (11-55 years of age) in the Menactra group (Group IV) and a percentage of subjects experiencing at least one severe systemic reaction equal to 5% in both groups, the power to demonstrate non-inferiority for safety is equal to 99%. (α=0.025).

6.10 Documentation of Study Findings

The sponsor will supply a set of CRF collations. The CRFs do not require carbon paper. The investigator must retain the bottom copy, and all other copies will be returned as directed by the sponsor. Instructions on how to complete these forms will be given to the investigator.

All study data must be entered by the investigator who will sign and date the CRFs. If the investigator authorizes other persons to make entries on the CRF, the names, positions, signatures and initials of these persons must be supplied to the sponsor (e.g. a sub

investigator might join the study after the site initiation visit and be authorized by the investigator to sign the CRFs).

All entries in the CRFs must be made *legibly* in black ball-point pen (*not pencil, felt tip or fountain pen*).

No data will be reported directly on the CRFs without source documentation.

Details regarding the percentage of CRFs verified by source documentation by the Study Monitor will be included in the V59P13 Monitoring Plan.

For each enrolled subject a CRF collation must be signed and dated by the investigator named in the study protocol or on the FDA 1572 form. CRFs must be completed during/after each study visit. Arrangements will be made by the monitor to collect the CRFs on completion. No CRFs are to be mailed to the sponsor without specific authorization.

The investigator must give a reasonable explanation for all missing data.

If corrections are made to entries in the CRF by the investigator or designee, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made after review and signature by the investigator, he/she must confirm and endorse the changes by signing and dating the study termination CRF again.

As part of the conduct of the trial, Novartis may have questions about the case report form data after the CRFs are collected from the site. These questions will be documented using Data Clarification Forms (DCFs). Novartis will answer the question if the answer is self-evident on "internal" DCFs, but the investigator will need to review these changes. If the DCF is not self-evident, Novartis will ask the investigator to provide the answer on an "external" DCF and sign it. Novartis will send the investigator a copy of each completed internal DCF. The investigator will review them and if he/she disagrees with the resolution, he/she will notify the site monitor, who will then generate a new DCF documenting the investigator's correction. The investigator will be requested to file each of the DCFs (both levels) for the trial.

Definitions of the DCF types are as follows:

Internal DCF: A query for which the resolution is self-evident. It can be answered without changing the meaning of the data or using logical numeric flow (for example, if an adverse event number is missing, the next number in sequence can be assigned). Internal corrections are defined in either the assumptions for internal queries guideline or in study-specific internal assumptions. The Clinical Data Coordinator or the Study Monitor can answer an internal DCF. Key safety (e.g. adverse event relationship) or primary endpoint data queries are not to be handled as an internal DCF.

External DCF: A query that requires information from the investigator. Key safety (e.g. adverse event relationship) or primary endpoint data queries must be handled as an external DCF.

6.11 Record Retention

Investigators must retain all study records required by Novartis and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

6.12 Use of Information and Publication

Novartis Vaccines and Diagnostics recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement.

7. REFERENCE LIST

1. Andersen BM. Mortality in meningococcal infections. Scand J Infect Dis 1978;10:277-82.

2. De Wals P, Hertoghe L, Reginster G, Borlee I, Bouckaert A, Dachy A, et al. Mortality in meningococcal disease in Belgium. J Infect 1984;8(3):264-73.

3. Halstensen A, Pedersen SH, Haneberg B, Bjorvatn B, Solberg CO. Case fatality of meningococcal disease in western Norway. Scand J Infect Dis 1987;19(1):35-42.

4. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81(4):536-8.

5. Campagne G, Chippaux JP, Djibo S, Issa O, Garba A. [Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger)]. Bull Soc Pathol Exot 1999;92(2):118-22.

6. Centers for Disease Control and Prevention. Laboratory-based surveillance for meningococcal disease in selected areas--United States, 1989-1991. Morbidity Mortality Weekly Report (MMWR); CDC Surveillance Summaries 1993;42 (SS-2):21-30.

7. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Carter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894-1901.

8. Ramsay M, Kaczmarski E, Rush M, Mallard R, Farrington P, White J. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev 1997;7(4):R49-54.

9. Decosas J, Koama JB. Chronicle of an outbreak foretold: meningococcal meningitis W135 in Burkina Faso. Lancet Infect Dis 2002;2(12):763-5.

10. Taha M-K, Bichier E, Perrocheau A, Alonso J-M. Circumvention of herd immunity during an outbreak of meningococcal disease could be correlated to escape mutation in the *porA* gene of *Neisseria meningitidis*. Infect Immun 2001;69(3):1971-1973.

11. du Chatelet IP, Alonso JM, Taha MK. [Clonal expansion of *Neisseria meningitidis* W135. Epidemiological implications for the African meningitis belt]. Bull Soc Pathol Exot 2002;95(5):323-4; discussion 324-5.

12. Rosenstein N, Fischer M, Tappero JW. Meningococcal Vaccines. Infectious Disease Clinics of North America 2001;15(1):155-169.

13. Centers for Disease Control and Prevention. Meningococcal disease and college students: Recommendations of the Advisory Committee on Immunization

Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2000;49(RR-7):13-20.

14. Cadoz M, Armand J, Arminjon F, Gire R, Lafaix C. Tetravalent (A, C, Y, W 135) meningococcal vaccine in children: immunogenicity and safety. Vaccine 1985;3(3):340-342.

15. King WJ, MacDonald NE, Wells G, Huang J, Allen U, Chan F, et al. Total and functional antibody response to a quadrivalent meningococcal polysaccharide vaccine among children. Journal of Pediatrics 1996;128(2):196-202.

16. Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. Pediatrics 1977;60(5):673-680.

17. Reingold AL, Hightower AW, Bolan GA, Jones EE, Tiendrebeogo H, Broome CV, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet 1985;2(July 20, 1985):114-118.

18. Käyhty H, Mäkelä PH, Peltola H. Immunological basis for PRP vaccines. In: Ellis RW, Granoff DM, editors. Development and Clinical Uses of Haemophilus b Conjugate Vaccines. New York, NY: Marcel Dekker Inc.; 1994. p. 1-18.

19. Rosenstein N, Perkins B. Update on *Haemophilus influenzae* serotype b and meningococcal vaccines. Pediatr Clin North Am 2000;47(2):337-352, vi.

8. SIGNATURE PAGE

Study title:
A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age

Study Number: V59P13

I have read the foregoing protocol and agree to conduct the clinical trial as outlined. I agree to conduct the trial in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____
Investigator Signature Date

Print name:_____

On behalf of Novartis Vaccines and Diagnostics, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical trial.

_____ _____
Medical Monitor Signature Date

Print name: _____

APPENDIX A: LIST OF CENTRAL LABORATORIES

The SBA analyses will be performed at:

Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany

Tel. +49 (0)6421-39-3439/3712
Fax. +49 (0)6421-39-5826

Other laboratories may be employed, as directed by the sponsor.

APPENDIX B: SHIPPING AND HANDLING OF LABORATORY SPECIMENS

PLEASE REFER TO STUDY MANUAL FOR DETAILS

1. Blood must be centrifuged, separated and frozen as soon as possible after collection. Make sure that coagulation is complete before separating the serum from blood components.

2. Please use the cryotubes provided. Be aware that the maximum-fill volume for these tubes is 90 % of rated capacity, i.e., 3.6 mL, to allow for expansion of the frozen serum. The tubes are marked with a maximum-fill line. Other sizes of cryotubes are not acceptable; if you have an inadequate supply, please contact your Monitor and additional tubes will be provided.

3. Close the tubes before freezing, and check to make sure that the caps are completely tight before packing for shipment.

4. Barcode labels are to be placed lengthwise down the tubes (not wrapped around). Barcodes are machine-readable only when their entire length runs along a flat surface. Please do not write on, make markings through, or otherwise deface the barcode. Make sure that labels are securely attached so that they do not pull away from the tubes after freezing. It is not necessary to fasten the label to the tube with adhesive tape.

5. Before the start of the trial, prepare separate cryoboxes for original and duplicate samples (“Original“ and “Duplicate” labeled cryotubes). After blood has been collected, centrifuged and separated, place labeled tubes in the respective labeled cryoboxes “Original“ and “Duplicate”. Keep the tubes in numerical order by subject number.

6. Freeze tubes at ≤ -18 °C (+/- 6°C) in an upright position so that serum does not come into contact with the cap. Tubes may be stored in any convenient position once they are frozen. Do not "quick-freeze" tubes by immersing them in either dry ice or liquid nitrogen; this may crack the tubes.

7. Pack cryotubes for shipment according to the instructions provided. If you have questions, please contact your Monitor.

8. Pack the original shipping log in an envelope inside the cardboard shipping box, on top of the Styrofoam insulated shipper. Fax the shipping log to:

Dr. Annette Karsten
Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Tel. +49 (0)6421-39-3439/3712
Fax. +49 (0)6421-39-5826

9. Duplicate samples should be sent still frozen after confirming the first shipment arrived safely.

APPENDIX C: SEROLOGY PROCEDURES

Retention of Study Records

The raw data, test records, and other laboratory documents generated during the course of the study will be retained in Clinical Serology, Novartis Vaccines, Marburg for 15 years

Quality Assurance Reviews

Quality Assurance of operations that are routinely performed may be carried out by means of process-based inspections. Technical review on all recorded stages of the assay data will be performed.

Objectives

To test human sera for the presence of bactericidal antibodies to:
N. meningitidis serogroups Men A, Men C, Men W-135, Men Y

Sample Storage

Frozen serum samples will be logged and stored at a temperature of minus 18°C ± 6°C in Clinical Serology, Novartis Vaccines, Marburg.

Test Methods and Procedures

Assay name: MenA-BCA
Antigen: *Neisseria meningitidis* serogroup A (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenC-BCA
Antigen: *Neisseria meningitidis* serogroup C (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenW-135-BCA
Antigen: *Neisseria meningitidis* serogroup W-135 (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenY-BCA
Antigen: *Neisseria meningitidis* serogroup Y (b) (4)

Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Equipment

Equipment as listed in the relevant Clinical Serology, SOP and associated documents.

Procedures

All procedures will be carried out according to the relevant SOPs and associated documents from Clinical Serology Marburg, Novartis Vaccines.

CLINICAL STUDY PROTOCOL V59P17

Amendment No 2

Issued 21 September 2007

Version number 3 **IND BB-IND 11278**

A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) when One Dose is Administered to Healthy Subjects 56-65 Years of Age

SPONSOR	Novartis Vaccines & Diagnostics, Inc 4560 Horton Street Emeryville, CA 94608-2916
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STUDY MONITOR	Alejandra Lanoël Phone number: +54 351 411 2307 E-mail: alejandra.lanoel@novartis.com
SPONSOR'S SIGNATORY	Peter Dull, MD

For trial related **emergencies out of office hours** please contact: +55 11 8524 5555

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Confidential

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STUDY SYNOPSIS

TITLE OF STUDY:

A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) when One Dose is Administered to Healthy Subjects 56-65 Years of Age

INVESTIGATOR(S) AND STUDY CENTER(S):

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Alejandra Valencia, MD
Centro de Investigación
Cientifica Alejandra Valencia
Avenida 9 116-20
Consultorio 806
Fundacion Santa Fe
Bogota, Colombia

STUDY PERIOD:

Approximately 9 months overall:
3 months of enrollment and 6 months of individual subject participation

CLINICAL PHASE:

Phase 3

RATIONALE:

Neisseria meningitidis causes life-threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been

identified, with serogroups A, B, C, W_{135} and Y being responsible for the large majority of invasive meningococcal infections worldwide.

Based upon the recent, successful development of conjugate vaccines designed to prevent disease with *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *N. meningitidis*, Novartis Vaccines is developing a conjugate meningococcal ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM_{197} (a non-toxic mutant of diphtheria toxin).

The primary objective of this phase 3 study is to assess the non-inferiority of safety and immunogenicity of Novartis MenACWY conjugate vaccine (MenACWY) to the US-licensed meningococcal ACWY conjugate vaccine (Menactra™) when administered to healthy subjects 19-55 years of age. MenACWY will also be compared to Menomune® in healthy subjects 56-65 years of age, an age group in which Menactra is not licensed.

MenACWY has been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 3200 subjects have received at least one dose of the final formulation of MenACWY being tested in this study. A comprehensive and detailed review of investigational MenACWY is contained in the Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

OBJECTIVES:

Primary Objective

Safety

To compare the percentage of subjects presenting at least one severe systemic reaction to the MenACWY with the percentage presenting at least one severe systemic reaction to Menactra during the first 7 days (Day 1-7) following a single dose administered to healthy subjects (19-55 years of age).

Secondary Objectives

Immunogenicity

1. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse, hSBA ≥ 1:4 or ≥ 1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.

2. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menactra, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs)

directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.

3. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menomune, defined as percentage of subjects with hSBA ≥ 1:4 or ≥ 1:8 or a seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

4. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menomune, as measured by hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

Safety

To describe and compare the percentages of subjects in the MenACWY and Menactra vaccine groups and the MenACWY and Menomune vaccine groups when administered to healthy adults aged 19 to 55 years and aged 56 to 65 years, respectively, in terms of:

Immediate hypersensitivity reactions (within 30 minutes) following vaccination

Local and systemic reactions during the period Study Day 1 – 7

AEs reported during the period Study Day 1- 29

Medically significant AEs reported during the period Study Day 30 - 180

Serious adverse events (SAEs) reported over the six-month follow-up period from Study Day 1 - 180

METHODS:

This is a phase 3, observer-blind multi-center, randomized, controlled study which is in healthy subjects 19-65 years of age.

Approximately 2500 healthy subjects 19-55 years of age (1250 subjects 19 to 34 years of age and 1250 subjects 35-55 years of age) will be randomly assigned to receive either MenACWY or Menactra. Immunogenicity testing will be done on the first 200 of the 19 to 34 years of age subgroup and on the first 200 of the 35 to 55 years of age subgroup; these subjects will be randomized in a 1:1 ratio. The remaining subjects will be randomized in a 2:1 ratio.

Subjects in the 56-65 years of age subgroup (450 total) will be randomized 2:1 MenACWY to Menomune and the initial 225 subjects will be tested for immunogenicity. (See Table 1)

Table 1 Vaccine Group and Immunogenicity Summary

	Total Subjects	**Subjects by Age Group Subjects enrolled** (Subjects for Immunogencity)		
Vaccine Group	**Subjects enrolled** (Subjects for Immunogenicity)	**19-34 yo**	**35-55 yo**	**56-65 yo**
MenACWY (Group I)	**1900** (350)	**800** (100)	**800** (100)	**300** (150)
Menactra (Group II)	**900** (200)	**450** (100)	**450** (100)	-
Menomune (Group III)	**150** (75)	-	-	**150** (75)
Total	**2950** (625)	**1250** (200)	**1250** (200)	**450** (225)

All Subjects:
At the enrollment visit (Visit 1, Study Day 1), the investigator, or a person designated by the investigator, should fully inform the subjects of all pertinent aspects of the trial and obtain informed consent. An initial physical assessment will be performed and relevant medical history, including the subject's last diptheria-containing vaccine, if within the past 5 years will be obtained. If the subjects are in good health according to the clinical judgement of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

An unblinded study vaccine administrator will give subjects their vaccinations. Subjects will be blinded to the study vaccine given. Subjects in Group I will receive a single dose of MenACWY administered intramuscularly (IM), subjects enrolled in Group II will receive a single dose of Menactra (comparator) administered IM and subjects in Group III will receive a single dose of Menomune (comparator) administered subcutaneously (SC). Subjects in the MenACWY and Menactra will be injected in the left upper deltoid and those in the Menomune group will be injected in the left upper deltoid. Following vaccination, the subjects will be monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, local injection site and systemic reactions.

Please refer to Table 2 for a summary of relevant medical history, safety assessments, and definitions. See Section 6.5.5 "Study Procedures and Flowchart" for greater detail.

During **Visit 1 (study day 1)**, subjects will be given a Diary Card and instructed on how to complete it for Study Days 1 – 29. In addition, they will be instructed on study procedures.

On **Study Day 3 (study days 3 - 5)**, study site personnel will contact subjects by telephone to remind them to record reaction data, any other medical problems, and use of concomitant

medication on the Diary Card. Study sites will record any medical problems reported by the subject that are of concern.

On **Study Day 29, (study days 29 - 43)**, all subjects will complete a medical office visit to assess their health status (see Table 2). A health assessment will be performed, including measurement of oral temperature and examination of previous injection site. Any new adverse events findings must be recorded onto the appropriate case report forms (CRFs). The Diary Card given at Visit 1 will be collected. Subjects will be given a worksheet and instructed on how to complete it for Study Days 30 - 180.

On **Study Day 180 (study days 152 - 208)**, study site personnel will contact all subjects by telephone to assess their health status and review any safety information recorded on the worksheet . Information from telephone interview will be recorded on subjects' CRFs.

Note: Home or office visits may be conducted instead of telephone calls at the discretion of the investigator.

Table 2: Summary of Relevant Medical History & Safety Assessments

Medical History: Any significant past diagnoses including allergies, injuries or hospitalizations with unresolved sequelae, major surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication, i.e. >2 weeks in duration or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	
• **Last diptheria containing vaccination, within the last 5 years**	
Immediate reaction Signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 min after vaccination
Local and systemic reactogenicity • **Temperature -** Oral temperature • **Local reactions -** Pain, erythema, inducation *If persisting beyond Day 7 will be reported as an AE* • **Systemic reactions -** Chills, nausea, malaise, myalgia, arthralgia, headache, rash *If persisting beyond Day 7 will be reported as an AE* **All adverse events**	For 7 days (Day 1 – 7)
Adverse events AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal	From Day 1 to Day 29
Medically significant adverse events AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal with the **exclusion** of pre-planned visits, medical office visits, or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis	From Day 30 to Day 180
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified.* *If SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 180
Medications: All prescription and non-prescription medications (with the exception of vitamin and mineral supplements)	For 7 days (Day 1 – 7)
Any prescription medication and antibiotics for treatment of reported AEs	From Day 1 to Day 180
Vaccinations, if any, administered during subject's participation in the study,	

should be recorded in the subject's CRF	

Immunogenicity subset:
At Visit 1 (Day 1), prior to administration of study vaccine, a blood sample (20 mL) will be obtained for serologic evaluation. An additional blood sample (20 mL) will be collected at Visit 2 (Day 29).

NUMBER OF SUBJECTS PLANNED:

Overall, the study will enroll 2950 subjects, of whom 625 will have immunogenicity testing. Approximately 2500 subjects 19-55 years of age will be randomly assigned to receive either one dose of MenACWY or one dose of Menactra. Approximately 450 subjects 56-65 years of age will be randomly assigned to receive one dose of MenACWY or one dose of Menomune.

SUBJECTS CHARACTERISTICS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Healthy male and female individuals 19-65 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are those:

1. who are 19-65 years of age inclusive and who, after the nature of the study has been explained have provided written informed consent (19-65 years of age)
2. who are available for all visits and telephone calls scheduled for the study;
3. who are in good health as determined by:
    - medical history
    - physical assessment
    - clinical judgment of the investigator

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling or unable to give written informed consent to participate in the study;
2. who are perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N. meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;

5. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) *(Exception: Receipt of OMP-containing Hib vaccines is permitted)*;
6. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;
7. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within one month after vaccination *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination)*
8. who have received a live viral vaccine within 60 days prior to enrollment;
9. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (≥38°C) within 3 days prior to enrollment;
10. who have any serious acute, chronic or progressive disease (e.g., any history of neoplasm, cancer, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition)
11. who are pregnant or nursing (breastfeeding) mothers or females of childbearing age who have not used or do not plan to use acceptable birth control measures (e.g. abstinence, oral or injected or implanted hormonal contraceptive, diaphragm or condom with spermicidal agent, intrauterine device) beginning 30 days before study entry and continuing through 180 days after the last vaccine dose. (Females will have a urine pregnancy test at entry, sensitive to 20 Iuβ-hCG)
12. who have epilepsy or any progressive neurological disease;
13. who have a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
14. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
    - receipt of immunostimulants
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study
15. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

16. who have Down's syndrome or other known cytogenic disorders;
17. who are planning to leave the area of the study site before the end of the study period;
18. who have a history of Guillain Barré Syndrome
19. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

TEST VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

The investigational MenACWY is obtained by extemporaneous mixing just before injection of the lyophilized Men A component with the Men CWY full liquid vaccine.

After reconstitution the MenACWY will have the following composition per 0.5 mL of injectable solution (See Table 3):

Table 3: MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

One 0.5 mL dose of MenACWY will be administered by intramuscular (IM) injection in the left upper deltoid.

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Licensed meningococcal ACWY conjugate vaccine Menactra™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single 0.5 mL dose formulated in sodium phosphate buffered isotonic sodium chloride solution to contain µg each of meningococcal

A, C, Y and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. (See Table 4)

Table 4: Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	4 µg
Serogroup C polysaccharide (PS)	4 µg
Serogroup Y polysaccharide (PS)	4 µg
Serogroup W135 polysaccharide (PS)	4 µg
Diphtheria toxoid protein total (Each PS is conjugated to diphtheria toxoid)	48 µg
Sodium phosphate	(b) (4)
Sodium chloride	(b) (4)

One 0.5 mL dose of Menactra will be administered by IM injection in the left upper deltoid.

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Menomune® (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single dose (one vial of vaccine and one vial of diluent). The vaccine consists of four meningococcal capsular polysaccharide serogroups (A, C, Y and W-135). After reconstitution with the liquid diluent, Menomune® will have the following composition per 0.5 mL of injectable solution (See Table 5):

Table 5: Menomune Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	50 µg
Serogroup C polysaccharide (PS)	50 µg
Serogroup W-135 polysaccharide (PS)	50 µg
Serogroup Y polysaccharide (PS)	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: WFI	Qs to 0.5 mL

One 0.5 mL dose of Menomune® will be administered subcutaneously in the left upper deltoid.

NOTE: Because study and control vaccines have different appearance in the syringe and different reconstitution requirements, different personnel will perform vaccine administration and safety assessments to ensure blinding.

CONCOMITANT VACCINES:

No concomitant vaccines will be administered during Visit 1.

The following vaccines are allowed if given at least one month after study vaccination:

- Normal routine or catch-up vaccinations appropriate for this age group.
- Recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination).*

Vaccinations will be reported as concomitant medications on the subject's CRF.

MEASURES OF IMMUNOGENICITY:

The ability of MenACWY to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Activity, hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed.

MEASURES OF SAFETY:

The measures of safety to be used in this study consist of local and systemic reactions and other adverse events.

SEROLOGY:

The SBA analyses will be performed at:

Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone: +49 (0)6421 39 3439/3712

Other laboratories may be employed, as directed by the sponsor.

CRITERIA FOR ASSESSING IMMUNOGENICITY OBJECTIVES:

The ability of MenACWY to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Assay, hSBA) will be measured.

Immunogenicity will be assessed using the following variables:

- Percentage of subjects with seroresponse. Seroresponse is defined as a hSBA ≥1:8 if the subject has hSBA < 1:4 at baseline. If the subject is ≥1:4 at baseline, then seroresponse is defined as the subject achieving a titer post injection of at least four times the subject's baseline hSBA titer.

- Percentage of subjects with hSBA ≥1:4 and hSBA ≥1:8.

- Geometric Mean Titers (GMTs), as measured by hSBA, and geometric mean ratio (GMR) of GMTs from one month after vaccination (Day 29) to baseline (Day 1)

Seroresponse

Immunogenicity of the MenACWY group (Group I) will be considered non-inferior to the immunogenicity of the Menactra group (Group II), for each of the four serogroups, if the lower limit of the two-sided 95% confidence interval (CI) for the difference between the groups (MenACWY group minus Menactra group) in the percentage of subjects with seroresponse in hSBA for that serogroup is greater than -10% at one month after vaccination, when administered to healthy subjects 19 to 55 years of age. The statistical superiority of MenACWY in comparison to Menactra will also be assessed for any given serogroup. A MenACWY serogroup will be considered to have statistically significantly higher immune response compared to that same serogroup of Menactra if the lower limit of the two-sided 95% CI around the difference in percentage of subjects with seroresponse in hSBA (MenACWY *minus* Menactra) is greater than 0, i.e., the CI does not include zero. The combined hypothesis testing for non-inferiority and statistical superiority does not require any adjustment for multiplicity.

GMTs

Immunogenicity of the MenACWY group will be considered non-inferior to the immunogenicity of the Menactra group if the lower limit of the two-sided 95% confidence interval on the ratio of the MenACWY to Menactra GMTs, as measured by hSBA is ≥0.5 at one month after vaccination, when administered to healthy subjects 19 to 55 years of age. The geometric mean ratio (GMR) will also be calculated.

Additional assays to further characterize the immune response to the vaccine components may also be performed (e.g., enzyme-linked immunosorbent assay [ELISA]).

CRITERIA FOR ASSESSING SAFETY OBJECTIVES:

MenACWY will be considered non-inferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% confidence interval for the difference between the groups (pMenACWY - pMenactra) is less than 6%, where pMenACWY and pMenactra are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1–Day 7) after vaccination in the MenACWY group (Group I), and the Menactra group (Group II).

STATISTICAL HYPOTHESIS:

Immunogenicity

The null hypothesis associated with the non-inferiority immunogenicity objective is that for at least one of the four serogroups, the lower limit of the two-sided 95% confidence interval (CI) for the difference between the groups (MenACWY group *minus* Menactra group) in the percentage of subjects with a seroresponse for that serogroup is ≤ -10% at one month after vaccination, when administered to healthy subjects 19 to 55 years of age.

Primary Safety

The null hypothesis associated with the primary safety objective is that the upper limit of the two-sided 95% confidence interval (CI) for the difference in proportions between the groups ($p_{MenACWY} - p_{Menactra}$) is ≥ 6%, where $p_{MenACWY}$ and $p_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1 – Day 7) after vaccination with MenACWY and Menactra , respectively for healthy subjects 19 to 55 years of age. In statistical notation:

H_0: $(P_{MenACWY} - P_{Menactra}) \geq 6\%$

H_a: $(P_{MenACWY} - P_{Menactra}) < 6\%$

This study will be considered successful if the null hypothesis for this primary safety objective is rejected.

STATISTICAL POWER CONSIDERATIONS:

Immunogenicity

In Novartis Study V59P6, conducted in adolescents 11-17 yoa, the observed estimates of the percentage of subjects in the MenACWY and Menomune groups with hSBA seroresponse for each serogroup are shown in Table 6.

Table 6: Percentage of Subjects in the MenACWY and Menomune Groups for Each Serogroup with hSBA Seroresponse as Observed in Novartis Study V59P6

	Seroresponse in hSBA	
Serogroup	MenACWY N=146-148	Menomune N=173-179
A	81%	41%
C	75%	54%
W	85%	71%
Y	86%	66%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in Rabbit Complement SBA (rSBA).

Given these results, we assume that for each serogroup the percentage of subjects with hSBA seroresponse is 0%, 5%, or 10% higher in the MenACWY group compared to the Menactra group. Table 7 below shows, for each serogroup, the number of subjects that need to be tested by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 7: Number of Subjects to be Tested by hSBA for 90% Power to Demonstrate Non-inferiority for Serogroups A, C, W and Y, Given Estimated Percentages of Subjects with Seroresponse in hSBA in MenACWY and Menactra groups

Serogroup	Percent of subjects with Seroresponse in hSBA MenACWY group (Group I)	Percent of subjects with Seroresponse in hSBA Menactra group (Group II)	Number of subjects evaluated in each group in order to have 90% power
A	75%	75%	395
	80%	75%	163
	80%	70%	98
	81%	76%	158
C	70%	70%	442
	75%	70%	186
	75%	65%	110
	80%	80%	337

W, Y	80%	80%	337
	85%	80%	135
	85%	75%	93
	85%	85%	268
	86%	81%	129

(b) (4) **version** (b) (4) **was used to perform the calculations, one sided α=0.025)**

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%

Table 8 below shows the power for several sample sizes to demonstrate non-inferiority for serogroups A, C, W, Y given estimated percentages of subjects with seroresponse in hSBA in the MenACWY and Menactra groups.

Table 8: Sample Sizes in the MenACWY and Menactra Groups to Demonstrate Non-Inferiority with High Power for Serogroups A, C, W, Y Given Estimated Percentage of Subjects with hSBA Seroresponse

	MenACWY Group		Menactra Group		
Serogroup	Percentage with Seroresponse in hSBA	N / Group	Percentage with Seroresponse in hSBA	N / Group	Power for Non-Inferiority
A	75%	170	75%	170	56%
	80%	170	75%	170	91%
	80%	170	70%	170	99%
	81%	170	76%	170	92%
C	70%	170	70%	170	52%
	75%	170	70%	170	87%
	75%	170	65%	170	98%
	80%	170	80%	170	63%
W, Y	80%	170	80%	170	63%
	85%	170	80%	170	95%
	85%	170	75%	170	99%
	85%	170	85%	170	73%
	86%	170	81%	170	96%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Again, we assume that, for each serogroup, the percentage of subjects in the 19 to 55 yoa adult group with hSBA seroresponse is 5% higher in the MenACWY group compared to Menactra. From Table 8 above, with 170 evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity primary objective and demonstrate non-inferiority is 92%, 87%, 95% and 96% for serogroup A, C, W, and Y respectively. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority is equal to 73%.

Employing the serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs), immunogenicity of the MenACWY group will be considered non-inferior to the immunogenicity of the Menactra group if the lower limit of the two-sided 95% confidence interval of the ratio of the MenACWY to Menactra GMTs, as measured by hSBA, is ≥0.5 at one month after vaccination, when administered to healthy subjects 19 to 55 years of age. The within group standard deviation for the log10 hSBA titers was assumed equal to 0.73 for serogroup A, 1.06 for serogroup C, 0.65 for serogroup W, and 0.80 for serogroup Y. These estimates were obtained, respectively, as the square root of the upper limit of the 80% CI of the within group variance observed for each serogroup in the previous Novartis MenACWY V59P6 study.

Table 9 below shows the power to demonstrate non-inferiority for this secondary objective for each serogroup using the standard deviations for each serogroup, highest:lowest GMT ratio, and sample sizes determined above for testing the primary null hypothesis.

Table 9: Power Calculations for Showing Non-Inferiority of MenACWY to Menactra Using the Lower Limit of the Two-Sided 95% CI on the ratio of the MenACWY to Menactra hSBA GMTs for Each Serogroup and Selected Group Sizes from Table 8

Serogroup	Highest:Lowest GMT Ratio	MenACWY N Per Group	Menactra N Per Group	Power for Non-Inferiority
A	1.0	170	170	96%
	1.2	170	170	79%
C	1.0	170	170	74%
	1.2	170	170	48%
W	1.0	170	170	98%
	1.2	170	170	88%
Y	1.0	170	170	93%
	1.2	170	170	72%

With 170 evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity secondary objective for hSBA GMTs and demonstrate non-inferiority is 96%, 74%, 98%, 93% for A, C, W, and Y, respectively, assuming a true underlying highest: lowest GMT ratio of 1. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority using hSBA GMTs is equal to 75%.

Primary Safety

The primary safety null hypothesis is that the upper limit of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra groups ($p_{MenACWY} - p_{Menactra}$) is ≥ 6%. Table 10 below shows the power to demonstrate non-inferiority for safety for different percentages of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination.

Table 10: Power to Demonstrate Non-Inferiority for Safety for Different Percentages of Subjects Experiencing At Least One Severe Systemic Reaction During the First 7 Days after Vaccination

Percentages of Subjects Experiencing At Least One Severe Systemic Reaction		
MenACWY Group N=1900	Menactra Group N=900	Power for Non-Inferiority
2%	2%	99%
3%	3%	99%
4%	4%	99%
5%	5%	99%

Assuming a sample size of 1900 subjects in the MenACWY group (Group I) and 900 subjects in the Menactra group (Groups II) and percentage of subjects experiencing at least one severe systemic reaction equal to 5% in both groups, the power to demonstrate non-inferiority for safety is equal to 99%. (one-sided α=0.025). From a perspective of detecting uncommon local or systemic reactions, or AEs, Table 11 (below) gives the probabilities of observing at least one subject with one such event for either vaccine group for several underlying event rates.

Table 11: Probability of Observing At Least One Subject with an Uncommon Event in the MenACWY and Menactra Groups for Given Underlying Event Rate

Underlying Event Rate	Probability of observing at least one event in Group I (MenACWY) N=1900	Probability of observing at least one event in Group II (Menactra) N=900
1/100	>99.9%	>99.9%
1/200	>99.9%	98.9%
1/500	97.8%	83.5%
1/1000	85.0%	59.3%

INTERIM ANALYSIS:

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled "Interim Analysis in a Clinical Trial".

After all subjects have completed Visit 2, (one month after vaccination), a group-unblinded analysis may be performed to assess immunogenicity.

In addition, a preliminary analysis may be performed to assess safety after all subjects have completed Visit 2 (one month visit after vaccination, including local and systemic reactions and body temperature within 7 days of immunization).

The results of these analyses will not alter the course of the trial.

Table 12: TIME AND EVENTS

Visit Number	**1**	☎	**2**	☎
Study Day (window)	Day 1	Day 3 (Study Days 3 – 5)	Day 29 (Study Days 29 to 43)	Day 180 (Study Days 152 – 208)
Obtain Informed consent	X			
Medical History	X			
Physical Assessment[a]	X		X	
Obtain Blood Sample[e]	X		X	
Administer Study Vaccine[b]	X			
Injection-site Examination	X[b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications[c]	X		X	X
Serious Adverse Events[d]	X	X	X	X
Study Termination				X

Note: Day 1 is defined as day of study vaccination.

[a] The physical examinations at visits 1 (study day 1) should be performed by a study physician..
[b] All subjects will be observed in the clinic for 30 minutes after vaccination.
[c] Collect data on concomitant medications prescription and non-prescription through the first 7 days. Collect data on concomitant medications (prescription only) for treatment of reportable AEs throughout the entire study.
[d] Collect information regarding any SAE or any event resulting in a subject's early termination any time during the subject's study participation. A 6-month follow up call will be made to assess the occurrence of SAEs and medically significant adverse events (Please see definitions on TABLE 2 on page 7). Home or office visits may be substituted at the discretion of the investigator.
[e] For immunogenicity subset subjects only

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATIONS

AE	Adverse Event
AP	(Statistical) Analysis Plan
BCDM	Biostatistics and Clinical Data Management
CFR	Code of Federal Regulations
CRF	Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EDT	Electronic Data Transfer
EC	Ethics Committee
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
hSBA	Human Serum Bactericidal Antibody
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal ACWY Conjugate Vaccine
MITT	Modified Intention-To-Treat
OMP	Outer Membrane Protein
PP	Per Protocol
qs	Quantity Sufficient
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
WFI	Water For Injection
WHO	World Health Organization
yoa	Years of Age

Definitions of Terms

End of Trial: The End of Trial corresponds to the last visit of the last subject undergoing the trial (LSLV, Last Subject Last Visit).
Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. Novartis Vaccines and Diagnostics, Inc. is an affiliate of Novartis AG.
Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.
Local and Systemic Reactions: Selected local and systemic AEs are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within seven days after vaccination are herein termed "local and systemic reactions."
Month, Day: Study months are based upon 28-day cycles. The study day refers to the number of days after enrollment, with the day of first vaccination being designated day 1.
Serious Adverse Event: Any experience or reaction that suggests a significant hazard, contraindication, side effect, or precaution. These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital abnormality, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate medical judgment, may jeopardize the subject. Vaccine failure should also be considered as a serious adverse event (SAE).
Medical Monitor: The Medical Monitor is a physician designated by Novartis Vaccines to be readily available to advise on trial related medical questions or problems and provide the appropriate medical expertise on behalf of the sponsor required for the design and conduct of the trial.
Field Monitor/ Study Monitor/Clinical Research Associate (CRA): The person authorized by Novartis Vaccines to monitor clinical trial activities at the trial site. Study Monitor and CRA are used synonymously.

2. ETHICS

2.1 Approval of Study Protocol

Novartis Vaccines or the investigator will provide the ethics committee (EC) or institutional review board (IRB) with all appropriate material, including the informed consent document, according to the local regulation. The EC or IRB should also be asked for a written statement regarding the composition of the committee and should comply with GCP and with the applicable regulatory requirement(s). The trial will not be initiated until appropriate EC or IRB approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. Prior to enrollment, the sponsor and the investigator must exchange written confirmation that their ethical and legal responsibilities have been observed. The EC or IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. Appropriate reports on the progress of the study will be made to the EC or IRB and the sponsor by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the sponsor.

2.2 Ethical Conduct and Good Clinical Practice

This trial will be performed with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study is conducted, and applicable standard operating procedures (SOPs). Specifically, this trial is based on adequately performed laboratory and animal experimentation; the trial will be conducted under a protocol reviewed and approved by an EC or IRB; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed. A copy of the ICH GCP guidelines and of the Declaration of Helsinki will be included in the investigator's study file.

2.3 Informed Consent of Subject and Confidentiality

2.3.1 Informed Consent of Subject

Adult subjects:

The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject’s legal rights the information should include that access to original medical records and processing of coded personal information must be authorized. A person who is qualified according to applicable local regulations must conduct the informed consent discussion. The

subject should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).
If a subject is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject's rights was accurately explained to, and apparently understood by the subject and that informed consent was given freely.
The investigator will provide a copy of the signed informed consent to the subject and will maintain the original in the investigator's study file.
The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive EC's or IRB's approval before use.
The subject should be informed in a timely manner if new information becomes available that might affect the decision to participate in the clinical trial. The communication of this information should be documented.
Incapacitated adults:
The investigator is responsible for obtaining informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. The information about the trial must be given orally and in an understandable form to the legally acceptable representative. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject's legal rights the information should include that access to original medical records and processing of coded personal information must be authorized. A person who is qualified according to applicable local regulations must conduct the informed consent discussion. The subject's legally acceptable representative should have the opportunity to inquire about details of the trial and to consider participation.
The informed consent form (ICF) must be signed and dated by the subject's legally acceptable representative and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).
In addition, the subject should be informed about the trial according to his or her capacity of understanding. Oral and written information is provided. If possible, the subject should sign and personally date a written informed consent as affirmatively agreement to participate in the clinical trial. Depending on the subject's capability of assessing the given information and forming an opinion the subject's explicit wish to refuse participation must be respected, even if the legally acceptable representative gives consent. This applies also to the wish to withdraw from the trial.
If the subject or his/her legally acceptable representative is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this

case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject or his/her legally acceptable representative has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject's rights were accurately explained to, and apparently understood by the subject or the legally acceptable representative and that informed consent was given freely.

The investigator will provide a copy of the signed informed consent documents to the subject's legally acceptable representative, and will maintain the original(s) in the investigator's study file.

The written informed consent form and any other written information should be revised whenever important new information becomes available that may be relevant to the legally acceptable representative's and subject's consent. Any revised written informed consent form, and written information should receive EC's or IRB's approval before use.

The subject and the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

2.3.2 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor. Study findings stored on a computer will be subject to local data protection laws. The subject, or where applicable, the subject's legally acceptable representative(s) will be informed that representatives of the sponsor, EC or IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

The investigator or designee will maintain a personal list of subject numbers and subject identification codes to enable records to be found at a later date.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to trial initiation, the investigator at the site must provide to Novartis Vaccines & Diagnostics, Inc. a fully executed and a signed financial disclosure form. Financial Disclosure Forms must also be completed for all sub investigators listed on the Form 1572 who will be directly involved in the treatment or evaluation of research subjects in this trial.
The trial will be administered and monitored by employees or representatives of Novartis Vaccines. Study Monitors or Field Monitors will monitor the site on a periodic basis and perform verification of source documentation for each subject. The Medical Monitor will be readily available to provide appropriate medical expertise on trial related medical questions. Novartis Vaccines & Diagnostics, Inc Regulatory Affairs or Pharmacovigilance Department will be responsible for the timely reporting of serious adverse events (SAEs).

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4. INTRODUCTION

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease. Meningococcal disease causes high rates of morbidity and mortality even among patients who receive early antibiotic treatment. Meningococcal meningitis has a case fatality rate of 5% to 10%, and in meningococcal septicemia fatality rate can be as high as 20% to 40%. (1, 2, 3, 4, 5, 6)

Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified. Virtually all disease-associated isolates are encapsulated, with serogroups A, B, C, Y, and W-135 being responsible for the large majority of invasive meningococcal infections worldwide (4, 5, 7, 8, 9, 10, 11). The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. (12, 13) Currently there is no licensed vaccine in the United States for serogroup B, while there is an ACWY meningococcal polysaccharide vaccine, Menomune® (Sanofi Pasteur), licensed for use in children ≥ 2 years of age and an ACWY meningococcal conjugate vaccine, Menactra™ (Sanofi Pasteur), licensed for use in adolescents ≥ 11 years of age. As the polysaccharide vaccine induces a largely T-cell independent immune response, the duration of protection is limited (e.g., 2 to 4 years), and hyporesponsivness to repeated doses has been described. (14, 15, 16, 17)

Based upon the recent, successful development of conjugate vaccines designed to prevent disease with Haemophilus influenzae type b, Streptococcus pneumoniae, and *N. meningitidis* serogroup C, Novartis is developing a conjugate meningococcal ACWY vaccine (MenACWY) for use in infants through adults. (18, 19) This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, Y, and W conjugated to a protein carrier CRM197 (a nontoxic mutant of diphtheria toxin).

Phase II studies of the MenACWY conducted in infants in Canada and the UK have demonstrated that the vaccine is well tolerated and highly immunogenic following two or three doses administered during their routine infant vaccination schedule. MenACWY has also been tested in older age groups and has been shown to be well tolerated and immunogenic. Overall, more than 3200 subjects have received at least one dose of the final formulation of MenACWY being tested in this study.

The primary objective of this phase 3 study is to assess the non-inferiority of safety and immunogenicity of Novartis MenACWY conjugate vaccine (MenACWY) to the US-licensed meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine (Menactra™) when administered to healthy subjects 19-55 years of age. A comprehensive and detailed review of investigational MenACWY is contained in the Investigator's Brochure supplied by the Sponsor; this document should be reviewed prior to initiating the study.

5. STUDY OBJECTIVES

Primary Objective

Safety

To compare the percentage of subjects presenting at least one severe systemic reaction to the MenACWY with the percentage presenting at least one severe systemic reaction to Menactra during the first 7 days (Day 1-7) following a single dose administered to healthy subjects (19-55 years of age).

Secondary Objectives

Immunogenicity

1. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse, hSBA ≥ 1:4 or ≥ 1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.

2. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menactra, as measured by serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs) directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.

3. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menomune, defined as percentage of subjects with hSBA ≥ 1:4 or ≥ 1:8 or a seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

4. To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menomune, as measured by hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

Safety

To describe and compare the percentages of subjects in the MenACWY and Menactra vaccine groups and the MenACWY and Menomune vaccine groups when administered to healthy adults aged 19 to 55 years and aged 56-65 years, respectively, in terms of:

Immediate hypersensitivity reactions (within 30 minutes) following vaccination

Local and systemic reactions during the period Study Day 1 – 7

AEs reported during the period Study Day 1- 29

Medically significant AEs reported during the period Study Day 30 - 180

Serious adverse events (SAEs) reported over the six-month follow-up period from Study Day 1 - 180

6. OVERALL STUDY DESIGN

6.1 Overall Study Design and Plan – Description

6.1.1 Overall Study Design

This is a phase 3, observer-blind, multi-center, randomized, controlled study which is in healthy subjects 19-65 years of age.

Approximately 2500 healthy subjects 19-55 years of age (1250 subjects 19 to 34 years of age and 1250 subjects 35-55 years of age) will be randomly assigned to receive either MenACWY or Menactra. Immunogenicity testing will be done on the first 200 of the 19 to 34 years of age subgroup and on the first 200 of the 35 to 55 years of age subgroup; these subjects will be randomized in a 1:1 ratio. The remaining subjects will be randomized in a 2:1 ratio.

Subjects in the 56-65 years of age subgroup (450 total) will be randomized 2:1 MenACWY to Menomune and the initial 225 subjects will be tested for immunogenicity. (See Table 1)

Table 1 Vaccine Group and Immunogenicity Summary

	Total Subjects	**Subjects by Age Group Subjects enrolled** (Subjects for Immunogencity)		
Vaccine Group	**Subjects enrolled** (Subjects for Immunogenicity)	**19-34 yo**	**35-55 yo**	**56-65 yo**
MenACWY (Group I)	**1900** (350)	**800** (100)	**800** (100)	**300** (150)
Menactra (Group II)	**900** (200)	**450** (100)	**450** (100)	-
Menomune (Group III)	**150** (75)	-	-	**150** (75)
Total	**2950** (625)	**1250** (200)	**1250** (200)	**450** (225)

All Subjects:
At the enrollment visit (Visit 1, Study Day 1), the investigator, or a person designated by the investigator, should fully inform the subjects of all pertinent aspects of the trial and obtain informed consent. An initial physical assessment will be performed and relevant medical history, including the subject's last diptheria-containing vaccine, if within the past 5 years will be obtained. If the subjects are in good health according to the clinical judgement of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.

Subjects in Group I will receive a single dose of MenACWY administered intramuscularly (IM), subjects enrolled in Group II will receive a single dose of Menactra (comparator) administered IM and subjects in Group III will receive a single dose of Menomune (comparator) administered subcutaneously (SC). Subjects in the MenACWY and Menactra will be injected in the left upper deltoid and those in the Menomune group will be injected in the left upper arm. Following vaccination, the subjects will be monitored in the clinic for 30 minutes to evaluate for signs or symptoms of anaphylaxis, local injection site and systemic reactions.

Please refer to Table 2 for a summary of relevant medical history, safety assessments, and definitions. See Section 6.5.5 "Study Procedures and Flowchart" for greater detail.

During **Visit 1 (study day 1)**, subjects will be given a Diary Card and instructed on how to complete it for Study Days 1 – 29. In addition, they will be instructed on study procedures.

On **Study Day 3 (study days 3 - 5)**, study site personnel will contact subjects by telephone to remind them to record reaction data, any other medical problems, and use of concomitant medication on the Diary Card. Study sites will record any medical problems reported by the subject that are of concern.

On **Study Day 29, (study days 29 - 43)**, all subjects will complete a medical office visit to assess their health status (see Table 2). A health assessment will be performed, including measurement of oral temperature and examination of previous injection site. Any new adverse events findings must be recorded onto the appropriate CRFs. The Diary Card given at Visit 1 will be collected. Subjects will be given a worksheet and instructed on how to complete it for Study Days 30 - 180.

On **Study Day 180 (study days 152 - 208)**, study site personnel will contact all subjects by telephone to assess their health status and review any safety information recorded on the worksheet . Information from telephone interview will be recorded on subjects' CRFs.

Note: Home or office visits may be performed instead of telephone calls at the discretion of the investigator.

Immunogenicity subset:

At Visit 1 (Day 1), prior to administration of study vaccine, a blood sample (20 mL) will be obtained for serologic evaluation. An additional blood sample (20 mL) will be collected at Visit 2 (Day 29).

Table 2: Summary of Relevant Medical History & Safety Assessments

Medical History: Any significant past diagnoses including allergies, injuries or hospitalizations with unresolved sequelae, major surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication, i.e. >2 weeks in duration or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine.	
• **Last diptheria containing vaccination, within the last 5 years**	
Immediate reaction Signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 min after vaccination
Local and systemic reactogenicity • **Temperature -** Oral temperature • **Local reactions -** Pain, erythema, induction *If persisting beyond Day 7 will be reported as an AE* • **Systemic reactions -** Chills, nausea, malaise, myalgia, arthralgia, headache, rash *If persisting beyond Day 7 will be reported as an AE* **All adverse events**	For 7 days (Day 1 – 7)
Adverse events AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal	From Day 1 to Day 29
Medically significant adverse events AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal with the **exclusion** of pre-planned visits, medical office visits, or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis	From Day 30 to Day 180
Serious Adverse Events: *All SAEs will be monitored until resolution and/or the cause is identified.* *If SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	From Day 1 to Day 180
Medications: All prescription and non-prescription medications (with the exception of vitamin and mineral supplements)	For 7 days (Day 1 – 7)
Any prescription medication and antibiotics for treatment of reported AEs	From Day 1 to Day 180

Vaccinations, if any, administered during subject's participation in the study, should be recorded in the subject's CRF	

Data Monitoring Committee

An independent, external DMC will be established to monitor safety by performing scheduled analyses. The chairperson of the DMC will conduct a review of SAEs as described in the DMC Charter. The DMC will be comprised of experienced vaccine clinicians who are not investigators in the trial and a statistician experienced in the monitoring and evaluation of safety data. Before the start of the trial, a DMC charter will be established specifying rules and guidelines for assessing safety. The DMC and its biostatistics support group will have access to study-subject treatment assignments and to the results of the scheduled safety analyses to make recommendations regarding Novartis Protocol V59P17 and study continuation. Details of all DMC procedures will be documented in the DMC Charter.

6.1.2 Planned Duration of Study

Expected subject enrollment interval: 3 months

Duration of individual subject's participation: 6 months

Total duration of study: 9 months

End of Trial: A phone call at 6 months is the last scheduled contact for follow-up.

6.1.3 Premature Discontinuation of the Study

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study vaccines etc.) will be returned to the sponsor or destroyed by the site, at the sponsor's discretion.

6.1.3.1 Stopping/Pausing Rules

There are no predetermined stopping rules other than those described in section 6.1.3.

6.2 Discussion of Overall Study Design

This is a phase 3, observer blind, multi-center, randomized, controlled study in healthy subjects 19-65 years of age.

The primary objective of this study is to assess the safety and immunogenicity of Novartis MenACWY conjugate vaccine (MenACWY). Because the only licensed quadrivalent conjugate vaccine (Menactra) is licensed only up to 55 years of age, the licensed quadrivalent polysaccharide meningococcal vaccine (Menomune) will be used to maintain blinding for subjects aged 56-65 years. The assessment of local reactogenicity profile of the vaccine will be done using a subset of the total enrolled subjects (identical to the immunogenicity subset).

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Healthy male and female individuals 19-65 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are those:

1. who are 19-65 years of age inclusive and who, after the nature of the study as been explained have provided written informed consent
2. who are available for all visits and telephone calls scheduled for the study;
3. who are in good health as determined by:
    - medical history
    - physical assessment
    - clinical judgment of the investigator

Informed consent must be obtained for all the subjects before enrollment into the study.

6.3.2 Exclusion Criteria

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling or unable to give written informed consent to participate in the study;
2. who are perceived to be unreliable or unavailable for the duration of the study period;
3. who had a previous or suspected disease caused by *N. meningitidis*;
4. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
5. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) *(Exception: Receipt of OMP-containing Hib vaccines is permitted)*;

6. who have received any investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to the completion of the study;
7. who have received any licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated within one month after vaccination *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination)*
8. who have received a live viral vaccine within 60 days prior to enrollment;
9. who have experienced within the 7 days prior to enrollment significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (≥38°C) within 3 days prior to enrollment;
10. who have any serious acute, chronic or progressive disease (e.g., any history of neoplasm, cancer, diabetes, cardiac disease, autoimmune disease, HIV infection or AIDS, or blood dyscrasias, with signs of cardiac or renal failure or severe malnutrition);
11. who are pregnant or nursing (breastfeeding) mothers or females of childbearing age who have not used or do not plan to use acceptable birth control measures (e.g. abstinence, oral or injected or implanted hormonal contraceptive, diaphragm or condom with spermicidal agent, intrauterine device) beginning 30 days before study entry and continuing through 180 days after the last vaccine dose. (Females will have a urine pregnancy test sensitive to 20 Iuβ-hCG at entry);
12. who have epilepsy or any progressive neurological disease;
13. who have a history of any anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
14. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):
    - receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
    - receipt of immunostimulants
    - receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study
15. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
16. who have Down's syndrome or other known cytogenic disorders;
17. who are planning to leave the area of the study site before the end of the study period;
18. who have a history of Guillain Barré Syndrome;

19. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

6.3.3 Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

For any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial the site will:

- Maintain contact with the pregnant subject,
- Complete a "Pregnancy Report" CRF as soon as possible,
- Obtain pregnancy outcome information for "Pregnancy Follow-up" CRF.

All subjects will be clinically monitored after withdrawal, the cause of which will be recorded in detail on the “Study Termination” CRF, “Adverse Events” CRFs and, where appropriate, on the subject’s medical records. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section 6.5.4.

Whenever possible, the tests and evaluations listed for the termination visit will be carried out.

Withdrawn subjects will not be replaced.

6.4 Vaccines

6.4.1 Vaccines Administered

Adults will be assigned MenACWY, Menactra or Menomune according to the group to which they have been assigned (See Table 1).

a) Investigational vaccine: MenACWY

The investigational Novartis Meningococcal ACWY conjugate (MenACWY) vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the Men CWY component.

One 0.5 mL dose of MenACWY will be administered by intramuscular (IM) injection in the left deltoid area.

b) Control vaccine: Menactra,

One 0.5 mL dose of Menactra will be administered by intramuscular (IM) injection in the left deltoid area.

c) Control vaccine: Menomune

One 0.5 mL dose of Menomune will be administered by subcutaneous (SC) injection in the left upper arm.

NOTE: Because study and control vaccines have different appearance in the syringe and different reconstitution requirements, different study personnel will perform vaccinations and safety assessments, respectively, to ensure blinding.

6.4.2 Identity of Investigational Vaccine

6.4.2.1 Vaccine Composition

Novartis MenACWY Conjugate Vaccine

After reconstitution the MenACWY vaccine will have the following composition per 0.5 mL of injectable solution (See Table 3):

Table 3: MenACWY Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY, (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

Menactra

Licensed meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine Menactra™ (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as a single 0.5 mL dose formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. (See Table 4)

Table 4: Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	4 µg
Serogroup C polysaccharide (PS)	4 µg
Serogroup Y polysaccharide (PS)	4 µg
Serogroup W135 polysaccharide (PS)	4 µg
Diphtheria toxoid protein total (Each PS is conjugated to diphtheria toxoid)	48 µg
Sodium phosphate	(b) (4)
Sodium chloride	(b) (4)

Menomune

Licensed Menomune® (manufactured by Aventis Pasteur Inc., Swiftwater, PA) is supplied as two vials: one vial containing a single dose of lyophilized meningococcal capsular polysaccharide serogroups Men A, C, Y, and W-135 combined component and the second vial containing the diluent. The contents of the lyophilized Menomune® vial are to be reconstituted with the diluent.

After reconstitution, Menomune® will have the following composition per 0.5 mL of injectable solution (See Table 5):

Table 5: Menomune Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	50 µg
Serogroup C polysaccharide (PS)	50 µg
Serogroup W-135 polysaccharide (PS)	50 µg
Serogroup Y polysaccharide (PS)	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: WFI	Qs to 0.5 mL

6.4.2.2 Vaccine Labeling, Storage and Packaging

All study vaccine supplies must be stored between 2 and 8°C (36-46°F). Do not freeze. Vaccines that have been stored differently from the sponsor's recommendations **must not** be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor. Batches of commercially available comparator vaccines must be stored separately from normal hospital/practice stocks in accordance with the instructions of the manufacturer.

The sponsor will supply the investigational and control vaccines (if available). The investigator (or designee) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.

Novartis Vaccines MenACWY vaccine is identified by a lot number. The last digit of the lot number is a letter that can differ within the same vaccine batch in case multiple packaging and/or labeling processes are performed. This has no impact on the vaccine composition or manufacturing process.

Novartis MenACWY Conjugate Vaccine will be supplied and packaged as a single dose per box. Each box will contain one vial and one pre-filled syringe. The vial will contain the lyophilized powder of the Men A component and the pre-filled syringe will contain the liquid solution of the Men CWY component.

For each study vaccine, the box label contains the vaccine identifier and the following information:

Protocol Number:
Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at 2-8°C
For Clinical Trial use only
Expiry date:
Lot number:
Sponsor name:

The Men A vial label will include the identity of the investigational product, a 6-digit blank to be completed with the subject number following randomization, the protocol number, the expiry date, the lot number, the required storage conditions, the cautionary statement "For clinical trial use only", and the directions for use.

The label for the pre-filled syringe containing Men CWY will include the same information as the vial label except the subject number.

Menactra

Menactra will be provided to the site by Novartis. All study vaccine must be stored at 2°C to 8°C (36°F to 46°F) in a monitored, temperature-controlled refrigerator housed in a secure area of the study site until ready for administration by personnel. Do not freeze.

The commercial label for Menactra will remain intact. Novartis will provide a separate box with the V59P17 protocol label to include individual labels for the syringe and drug accountability log. The label will include:

Protocol Number:
Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at 2-8°C
For Clinical Trial use only
Expiry date:
Lot number:
Sponsor name:

Place the used, empty Menactra and diluent vials into the box supplied by Novartis.

Menomune

Menomune will be provided to the site by Novartis. All study vaccine must be stored at 2°C to 8°C (36°F to 46°F) in a monitored, temperature-controlled refrigerator housed in a secure area of the study site until ready for administration by personnel. Do not freeze.

The commercial label for Menomune will remain intact. Novartis will provide a separate box with the V59P17 protocol label to include individual labels for the syringe and drug accountability log. The label will include:

Protocol Number:
Vaccine description:
Quantity of dosage units, composition, route of administration:
Store at 2-8°C
For Clinical Trial use only
Expiry date:

Lot number:
Sponsor name:

Place the used, empty Menomune and diluent vials into the box supplied by Novartis.

6.4.2.3 Vaccine Administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in the Study Manual. Only unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site will administer all vaccines.

Novartis MenACWY Conjugate Vaccine

The vaccine must be **well shaken** and visually inspected before use. The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol). Before vaccination, the skin must be dry. **DO NOT inject intravascularly**.

In the event that any of the vaccine dosing units is damaged, unusable, or has been stored or exposed to temperatures outside the permitted range, a replacement set (as appropriate to randomization) should be supplied.

Menactra Conjugate Vaccine

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the deltoid region. Before injection, the skin at the injection site should be cleaned and prepared with a skin disinfectant.

Menactra should not be administered intravenously, subcutaneously, or intradermally.

Potential drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

Menomune Polysaccharide Vaccine

Menomune® vaccine should be administered as a single 0.5 mL injection by the **subcutaneous** route into the left upper arm. Before injection, the skin at the injection site should be cleaned and prepared with a skin disinfectant.

Potential drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines or to individuals with a history of allergy to mercury-containing

compounds, such as sodium ethylmercurithiosalicylate. Neither MenACWY nor Menactra include mercury-containing compounds. Menomune supplied as a single dose does not include mercury- containing compounds.

Any oral temperature ≥ 38°C or serious active infection is reason for delaying vaccination. Vaccination should also be delayed according to instructions in section 6.3.3.

Standard vaccination practices should be observed and care should be taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4.3 Method of Assigning Subjects to Vaccination Groups

Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 6-digit subject number.The first two digits identify the study site, for example “01”. The next four digits identify the subject within the site and will be assigned sequentially, for example “0001” as the first subject enrolled.

Subjects who meet the initial study inclusion and no exclusion criteria will be randomly assigned to receive either MenACWY or Menactra/Menomune . Approximately 2600 healthy subjects 19-55 years of age (1300 subjects 19 to 34 years of age and 1300 subjects 35-55 years of age) will be randomly assigned to receive either MenACWY or Menactra within each study site and age group. Immunogenicity testing will be done on the first 400 of the 19 to 34 years of age subgroup and on the first 400 of the 35 to 55 years of age subgroup; these subjects will be randomized in a 1:1 ratio. The remaining subjects will be randomized in a 2:1 ratio. Subjects in the 56-65 years of age subgroup (450 total) will be randomized 2:1 MenACWY to Menomune and the initial 225 subjects will be tested for immunogenicity. (See Table 1).

IVRS will be used for randomization of subjects. Additional information will be provided in the Study Manual.

6.4.4 Selection of Doses in the Study

The doses used in this study are based upon dose and formulation finding studies conducted in toddlers in Finland, Germany and the United States. In one trial (Finland and Germany), more than 500 toddlers received at least one dose of one of 5 formulations of MenACWY (approximately 100 subjects per group). While all formulations were well tolerated and immunogenic, the formulation used in this trial appeared to provide optimal responses for Serogroup A relative to all other formulations.

In another trial conducted in the US, 235 toddlers received one dose of three formulations of investigational MenACWY conjugate vaccine; two formulations without adjuvant at a fixed dose of 5 µg or 10 µg per oligosaccharide antigen and one formulation of 5 µg per oligosaccharide adjuvant with aluminum phosphate adjuvant. Although preliminary data suggested improved immunogenicity (as measured by GMTs) for at least one vaccine antigen component (W) in the presence of adjuvant, there was no apparent difference in the responses to the other antigens (A, C and Y). A subsequent study in toddlers (V59P7) supported the conclusion that addition of the adjuvant provided no meaningful improvement in immunogenicity. For additional information, please see the Investigator Brochure.

6.4.5 Blinding

The trial will be performed as an observer-blind study. The designated nurse(s) or physician(s) will be responsible for administering the study vaccines to the subjects, and will be instructed not to reveal the identity of the study vaccines either to the subject nor to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the trial, except in an emergency. This (these) designated individual(s) will have no contact with the subjects after the administration of the study vaccine. If the study vaccine code is supplied to the investigator in the event of an emergency, the investigator must notify the study monitor immediately. The date and time, along with the reason for the unblinding, should be noted. Study vaccine codes will not be freely available to the investigator or personnel monitoring the trial until after the completion of the trial and final data review. Sponsor and subjects will be blinded to treatment. An IVRS vendor external to the sponsor (who will perform the randomization) and individuals involved in drug packaging will be unblinded.

6.4.6 Prior and Concomitant Therapy

All prescription medication and antibiotics, including non-study vaccines, being taken by the subjects on entry to the study and prescription medication and antibiotics given in addition to the study vaccine during this clinical trial are to be regarded as concomitant medication and must be documented on the “Concomitant Medications” CRFs. If therapy was started prior to the beginning of the study, the box titled “prestudy” under the “start date” field on the “Concomitant Medications” CRF should be checked.

CONCOMITANT VACCINES:

No concomitant vaccines will be administered during Visit 1.

The following vaccines are allowed if given at least one month after study vaccination:

- Normal routine or catch-up vaccinations appropriate for this age group
- Recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria *(Exception: Influenza vaccine may be administered up to 15 days prior to study vaccination and at least 15 days after study vaccination).*

Vaccinations will be reported as concomitant medications on the subject’s CRF.

6.4.7 Vaccination Compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator or designee will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be returned to the sponsor or destroyed at the investigational site according to the relevant Novartis SOP. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.4.8 Adherence to Randomization

Adherence to randomization will be verified by a designated and unblinded Study Monitor independent of the staff involved in the regular monitoring of the study by checking the randomization list against the vaccination records maintained at the study site.

An unblinded, appropriately qualified person, will prepare/administer the vaccine as indicated by IVRS for the individual subject. The blinded investigator or designate as well as the Study Monitor will not be unblinded during the conduct of the study.

6.5 Immunogenicity and Safety Variables

6.5.1 Immunogenicity and Safety Measurements Assessed

The Time and Events Table (Table 12) in the Synopsis and section 6.5.5 describe the required evaluations.

6.5.2 Appropriateness of Measurements

The measures of safety used in this study are routine clinical procedures. Selected local and systemic reactions are routinely monitored in vaccine clinical trials as indicators of reactogenicity. They will be closely followed and stringently reported.

6.5.3 Immunogenicity Variables

The ability of MenACWY vaccine to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (human Serum Bactericidal Activity, hSBA) will be measured.

Additional assays to further characterize the immune response to the vaccine components may also be performed.

6.5.4 Safety Variables

A brief medical history will be obtained and physical assessment/exam performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.1.1 and 6.5.5.

6.5.4.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, the study site investigator and Novartis Vaccines' Medical Monitor will make a clinical assessment as to whether continued follow-up of the AE is warranted.

The investigator will determine the severity of events reported on the "Adverse Events" CRF using the following definitions:

Mild:	no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The investigator will determine the relationship of the study treatment to an AE based on the following definitions:

<u>1. Not Related</u>

The AE is not related if exposure to the investigational vaccine has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The investigator will determine the relationship of the study treatment to an AE.

6.5.4.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Of note: a "possible vaccine failure" should be reported as a serious AE only if it resulted in an infectious disease that should have been prevented by the vaccine implied.

Adverse events that do not fall into these categories, are defined as **non-serious**.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history CRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

6.5.4.3 Local and Systemic Reactions

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post vaccination, will be recorded on the "Local and Systemic Reactions" rather than the "Adverse Events" CRF.

The assessment of local reactions will include: injection site pain, erythema, induration

The assessment of systemic reactions will include: chills, nausea, malaise, myalgia, arthralgia, headache, and rash.

The assessment of other indicators of reactogenicity will include: oral temperature, stayed home due to reaction, and use of analgesics/antipyretics.

6.5.4.4 Clinical Laboratory Tests

Clinical laboratory tests will not be required by the protocol.

6.5.4.5 Documentation/Monitoring/Reporting of Safety Variables

All study subjects will be observed for at least 30 minutes after vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena (such as rashes, itching, or other allergic manifestations). Each subject in the immunogenicity subset will be instructed to complete a diary card for 7 days following study vaccine administration, to describe local reactions, systemic reactions, and other selected indicators of reactogenicity. If a local and systemic reaction ends on day 7, it will be recorded on the "Local & Systemic Reactions" CRF. If it continues beyond 7 days after vaccination, it will be recorded on the "Adverse Events" CRF. All medically significant adverse events (Refer to Section 6.1.1 Table 2) must be reported and documented for all subjects. The period of observation for adverse events extends from the time the subject gives informed consent until he or she undergoes the final study examination. Any medical event that occurs after the Informed Consent Form is signed, but prior to receiving study vaccine and is related to a study procedure will be documented as an adverse event and recorded on the AE CRF. Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine and is not related to a study procedure will be documented as a pre-existing condition and will be recorded on the Medical History CRF.

The investigator will monitor all AEs, regardless of severity, until resolution. All subjects experiencing adverse events - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an "Adverse Events" CRF and on the "Vaccine Serious Adverse Event" form, if necessary, which is part of the investigator's study file. All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

In addition, any event resulting in a subject's withdrawal from study should be reported according to section 6.3.3 "Removal of Subjects from Therapy or Assesment". All SAEs which occur during the course of the trial, whether considered to be associated with the study vaccination or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor: Olga Mellone, MD
Phone number: +55 11 5532 2465
Mobile phone: + 55 11 9941 2469

Study Monitor: Alejandra Lanoël
Phone number: +54 351 411 2307

For trial related **emergencies out of office hours** please contact: +55 11 8524 5555

As far as possible, all points raised on the "Vaccine Serious Adverse Event" form need to be addressed and faxed immediately to the Medical Monitor or Study Monitor. The original form should be filed at the study site. The event must also be documented on the "Adverse Events" CRF. After receipt of the initial report, the Medical Monitor/Study Monitor will review the information and contact the investigator if it is necessary to obtain further information for assessment of the event. Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF(s) in addition to the outcome of the AE. Any serious or unexpected AE must be reported to the EC or IRB in a timely manner. Adequate documentation will be provided to the sponsor showing that the EC or IRB has been properly notified. The sponsor must also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious and non-serious adverse drug reactions to the regulatory authorities and the EC or IRB.

If required, a follow-up report including all new information obtained on the serious adverse event must be prepared and sent to the Medical Monitor/Study Monitor. The report should be marked "Follow-up report".

The investigator will submit, per institutional requirement, copies of all these reports to the EC or IRB and other relevant authorities.

Post-Study Events

Any AE occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine - and therefore a possible adverse drug reaction - must be reported.

6.5.5 Study Procedures and Flowchart

Informed consent must be obtained from the subject prior to the performance of any trial specific tests or evaluations, i.e., any unusual or non-routine procedures that involve risk, however trivial, to the subject.

Note: Home or office visits may be substituted for phone calls at the discretion of the investigator (e.g., phone contact is not possible).

Study Day 1: Screening/Baseline and Vaccination

Subjects should be screened prior to vaccination at Visit 1 to ensure they meet all inclusion and no exclusion requirements.

a) Fully inform the subjects of all pertinent aspects of the trial and obtain informed consent prior to the performance of any trial specific tests or evaluations, i.e. any unusual or non-routine procedures that involve risk, however trivial to the subject.
b) Obtain and record relevant medical history.
c) Investigator performs initial physical assessment including measurement of oral temperature, weight and height, and a check of general appearance and systems evaluation including physical exam of the heart, lungs, and abdomen. A urine pregnancy test will be conducted for all females of child-bearing potential.
d) If the subjects are in good health according to the clinical judgement of the investigator, and they meet all other inclusion criteria and no exclusion criteria, they may be enrolled in the study.
e) Obtain blood sample via venipuncture (20 mL) from all subjects in the immunogenicity subset.

Reason for delaying blood draw: Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

f) Unblinded site personnel will administer the study vaccine. Subjects will receive either MenACWY or Menactra/Menomune.
g) Observe subject in the clinic for 30 minutes.
h) Examine the injection site of the vaccine for local reactions at the end of the 30 minute observation period.

i) Instruct subjects in the evaluation of local and systemic reactions, and recording of oral temperature.
j) Dispense diary card and instruct subject on how to complete Diary Card for the Study Days 1 – 29.

Study Day 3 (Study days 3 - 5)

a) Study site personnel will contact subjects by telephone. The purpose of this contact is the following:
   - Remind the subject to record reaction data, any other medical problems, and use of concomitant medication on the Diary Card
   - Record any medical problems reported by the subject that is of concern.

Study Day 29, (Study days 29 - 43)

All subjects will complete a medical office visit to assess their health status. (See Table 2)
a) Perform a physical examination/assessment, including measurement of oral temperature and examination of previous injection site. Any new adverse findings must be recorded onto the appropriate CRFs.
b) Collect and review diary card with subject. Collect and record information regarding SAEs, events requiring a medical office visit, or any event resulting in a subject's early termination reported through Visit 2. Record information obtained on the appropriate CRFs.
c) Collect prescription medications used to treat reported adverse events. Record information obtained on the appropriate CRFs.
d) Obtain blood sample via venipuncture (20 mL) for subjects in the immunogenicity subset. Process blood and store serum for evaluation.
e) Dispense worksheet and instruct subject on how to complete it for Study Days 30-180.
f) Remind subject that they will be contacted in 5 months.

Study Day 180 (Study days 152-208)

Contact the subject by telephone to assess their health status and review any safety information recorded on the worksheet. Information from telephone interviews will be recorded on subjects' CRFs.

Table 12: TIME AND EVENTS

Visit Number	**1**	☎	**2**	☎
Study Day (window)	Day 1	Day 3 (Study Days 3 – 5)	Day 29 (Study Days 29 to 43)	Day 180 (Study Days 152 – 208)
Obtain Informed consent	X			
Medical History	X			
Physical Assessment[a]	X		X	
Obtain Blood Sample[e]	X		X	
Administer Study Vaccine[b]	X			
Injection-site Examination	X[b]		X	
Assess Local and Systemic Reactions and Body Temperature	X		X	
Concomitant Medications[c]	X		X	X
Serious Adverse Events[d]	X	X	X	X
Study Termination				X

Note: Day 1 is defined as day of study vaccination.

[a] The physical examinations at visits 1 (study day 1) should be performed by a study physician..
[b] All subjects will be observed in the clinic for 30 minutes after vaccination.
[c] Collect data on concomitant medications prescription and non-prescription through the first 7 days. Collect data on concomitant medications (prescription only) for treatment of reportable AEs throughout the entire study.
[d] Collect information regarding any SAE or any event resulting in a subject's early termination any time during the subject's study participation. A 6-month follow up call will be made to assess the occurrence of SAEs and medically significant adverse events (Please see definitions on TABLE 2 on page 7). Home or office visits may be substituted at the discretion of the investigator.
[e] For immunogenicity subset subjects only

6.5.5.1 Study Evaluations

Blood samples (for subjects in immunogenicity subset only) taken in the following time windows will be evaluable:

Pre-vaccination: Study Day 1

Post-vaccination: Study Day 29 (window: + 14 days)

6.5.5.1.1 Laboratory Assessments

Not applicable.

6.5.5.1.2 Labeling and Storage of Serum Samples for Serology

Twenty (20) mL of whole blood should be available to be processed for serum for use in assays.

The blood will be centrifuged on the same day and the serum will be distributed in two equal aliquots using the tubes provided. The aliquots will be stored at a temperature of minus 18°C or below.

Each serum tube will be labeled with an identifying bar code including subject number, and protocol number. Serum samples will be sent to the sponsor or will be collected by a representative of the sponsor.

For further information see Appendix B.

Complete instructions for labeling and storage of serum samples are included in the Study Reference Manual.

6.6 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained at the latest during the initiation visit. During each monitoring visit qualified staff representing the sponsor will perform source data verification. A CRF collation supplied by the sponsor will be completed for each subject. Trained delegates of the sponsor will check the entries.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor's Clinical Quality Assurance (CQA) department will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

6.6.1 Study Monitoring

The clinical study site will be monitored by regular site visits and telephone calls to the investigator by members of the Clinical Research department, the sponsor, or their agents following Novartis Vaccines' internal SOP and/or those procedures that are specified by Novartis Vaccines for monitoring trials. By frequent communication, the site monitor will ensure that the study is conducted according to the protocol.

CRFs and all original data collected at the site including subjects' medical records should be available for review during monitoring visits. During these visits, the site monitor should review drug accountability records and document retention including the Investigator's Study File. Additionally, the site monitor should check that clinical study procedures are observed and discuss any problems with the investigator.

6.6.2 Source Data Verification and Audits

Inspection and examination of CRFs and source documents (all original recordings, laboratory reports, medical records) - giving due consideration to data protection and medical confidentiality - will be undertaken by representatives of the sponsor. All data not recorded directly on the CRFs as defined in section 6.10 of this study protocol must be verified by checking CRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol. Source data verification will be performed and recorded following Novartis Vaccines' internal SOP. The subject or the subject's legally acceptable representative must also allow access to the subject's medical records. Each subject, or the subject's legally acceptable representative, will be informed of this prior to the start of the study.

During or after the clinical study, the regulatory authorities, the EC or IRB and/or representatives of the sponsor may request access to all source documents, CRFs and other study documentation for on-site audit or inspection.

6.7 Data Management

All CRF data (except for comments fields on the "Medical History" and "Comments" CRFs and the "Other, specify" item on the "Screen Log", if applicable), will be entered in duplicate into a (b) (4) database by BCDM, Novartis Vaccines.

Data validation will be performed using the programming languages (b) (4) (b) (4) Data quality assurance will be performed by doing a 100% check of all database updates resulting from the resolution of queries, and by estimating the database error rate with 95% upper confidence limit. The latter must be below the departmental accepted level of 0.5%. Analysis will be performed by BCDM using (b) (4) version (b) (4) according to a predefined Analysis Plan (AP), developed by the study Biostatistician.

All serology data analyzed by Clinical Serology Marburg, Novartis Vaccines will be entered into the (b) (4) database by Clinical Serology Marburg, Novartis Vaccines. All results will be checked in the laboratory for validity and completeness by three persons before access to the data is granted to BCDM, Novartis.

6.7.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

6.7.2 Data Protection

Novartis Vaccines & Diagnostics, Inc. respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

6.8 Changes in the Conduct of the Study or Planned Analysis

Planned changes in the conduct of the study will be described in protocol amendments; changes in the planned analysis will be described in the clinical study report.

An amendment is a written description of change(s) to or formal clarification of a study protocol.

The EC or IRB must be informed of all amendments and if necessary prior review and documented approval/favorable opinion must be sought for ethical aspects. Approval must also be obtained from the authorities, if necessary.

The sponsor, the investigator, the EC or IRB, and authorities if necessary will agree upon such amendment prior to implementation.

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical Plans

The statistical evaluation of the results will be performed by BCDM as predefined in the AP. The statistical tables and graphs will be generated using (b) (4) version (b) (4)

Baseline is defined as the time of first vaccination.

Definition of populations to be analyzed:

(a) All enrolled population

All subjects who:

- have data signed the inform consent and have been randomized

(b) Intention-to-treat (ITT) population, Immunogenicity

- All subjects in the enrolled population who:
  - actually receive a study vaccination, and
  - provide at least one evaluable serum sample before or after baseline

(c) Modified Intention-to-treat (MITT) population, Immunogenicity

- All subjects in the ITT population who:
  - actually receive a study vaccination, and
  - provide at least one evaluable serum sample [both before and after baseline]

(d) Per protocol (PP) population, Immunogenicity, e.g., also the population evaluable for immunogenicity

- All subjects in the MITT population who:
  - receive all the relevant doses of vaccine correctly, and
  - provide evaluable serum samples at the relevant time points, usually paired, and
  - have no major protocol deviation as defined prior to unblinding

A **major deviation** is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

(e) Exposed Population

- All enrolled subjects who:
  - actually receive a study vaccination

(f) Safety Population

- All subjects in the Exposed Population who:
  - provide post-baseline safety data

6.9.1.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group.

6.9.1.2 Analysis of Immunogenicity Criteria

The percentage of subjects with Seroresponse in hSBA and associated 95% Clopper-Pearson Confidence Intervals (CIs) will be computed for each serogroup and for each vaccination group.

A Seroresponse in hSBA titer for a subject is defined based on the pre-immunization titer. For a subject with a pre-immunization titer greater than or equal to 1:4, e.g., 1:x, seroresponse is achieved if the subject's post-immunization titer is 1:4x or greater. For a subject with a pre-immunization titer less than 1:4, a seroresponse in titer is achieved if the subject's post-immunization titer is 1:8 or greater.

The 95% CIs for the difference in proportions (given serogroup for MenACWY - given serogroup for Menomune) will be constructed using standard methods. If the CI is entirely to the right of -10%, then non-inferiority will be declared for that serogroup. Moreover, if the CI is entirely to the right of 0%, then superiority will be declared.

Immunogenicity of MenACWY group (Group I) will be considered non-inferior to the immunogenicity of Menactra group (Group II), for each of the four serogroups, if the lower limit of the two-sided 95% confidence interval (CI) for the difference between the groups (MenACWY group *minus* Menactra group) in the percentage of subjects with hSBA seroresponse for that serogroup is greater than -10%. The statistical superiority of MenACWY in comparison to Menactra will also be assessed for any given serogroup. A MenACWY serogroup will be considered to have a statistically significantly higher immune response to that same serogroup of Menactra if the lower limit of the two-sided 95% CI around the difference in percentage of subjects seroresponse in hSBA (MenACWY *minus* Menactra is greater than 0), i.e. the CI does not include zero. The combined hypothesis testing for non-inferiority and statistical superiority does not require any adjustment for multiplicity.

Geometric Mean Titer (GMT) at baseline (Day1) and at one month after vaccination (Day 29) and GMT increase (geometric mean ratio, [GMR]) at Day 29 as compared to baseline values (Day 1) will also be calculated for each serogroup (A, C, W and Y) and for each vaccine group. The GMTs, GMRs and 2-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) titers and their 95% CIs obtained from an Analysis of Variance (ANOVA) model with vaccination group and center as factors in the model. Statistical details for the use of this method and possibly others (e.g., Analysis of Covariance) will be provided in the (statistical) analysis plan. Titers below the limit of detection will be set to half that limit for the purposes of the analysis. This analysis will be performed for the 19-55 year age group.

6.9.1.3 Analysis of Safety Criteria

Primary Safety

The primary safety analysis is the comparison of the percentage of subjects presenting at least one severe systemic reaction to the Novartis MenACWY Conjugate Vaccine with the percent of subjects presenting at least one severe systemic reaction to the licensed Menactra™ vaccine during the first 7 days (Day 1-7) following a single dose administered to healthy subjects 19-55 years of age.

MenACWY will be considered non-inferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% confidence interval for the difference between the groups (pMenACWY - pMenactra) is less than 6%, where pMenACWY and pMenactra are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Day 1 - Day 7) after vaccination in the MenACWY group (Group I) and the Menactra group (Group II), respectively.

Secondary safety

Local and systemic reactions and oral temperature reported during the period Day 1 - Day 7 after vaccination.

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.
For the local and systemic reaction safety variables, differences among the vaccine groups after the vaccination with respect to all variables (including fever) will be analyzed by using Pearson's Chi-square test, or Fisher's Exact test where appropriate.

Erythema and induration will be categorized as none (0 mm), 1-25 mm, 26-50 mm and >50 mm. Oral temperature will be categorized as <38°C, 38-38.9 °C, 39-39.9°C and ≥ 40°C. All other systemic reactions will be categorized as none, mild, moderate and severe. Each local and systemic reaction will also be categorized as none versus any.

Other Adverse Events

All the adverse events occurring during the study, judged either as related to vaccination or not by the investigator, will be recorded as specified in Section 6.1.1.

The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group. When an adverse event occurs more

than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

6.9.1.4 Interim Analysis Planned

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled "Interim Analysis in a Clinical Trial".

6.9.1.5 Preliminary Analysis

After all subjects have completed Visit 2, one month after vaccination, a group unblinded preliminary analysis may be performed to assess immunogenicity.

In addition, a preliminary analysis may be performed to assess safety after all subjects have completed Visit 2 (one month visit after vaccination, including local and systemic reactions and body temperature within 7 days of immunization).

The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Novartis BCDM standard operating procedure entitled "Interim Analysis in a Clinical Trial."

6.9.2 Determination of Sample Size

Immunogenicity

In Novartis Study V59P6, conducted in adolescents 11-17 yoa, the observed estimates of the percentage of subjects in the MenACWY and Menomune groups with seroresponse in hSBA for each serogroup are shown in Table 6.9.2-1 below.

Table 6.9.2-1: Percentage of Subjects in the MenACWY and Menomune Groups for Each Serogroup with hSBA Seroresponse as Observed in Novartis Study V59P6

	Seroresponse in hSBA	
Serogroup	MenACWY N=147-148	Menomune N=152-158
A	81%	41%
C	75%	54%
W	85%	71%
Y	86%	66%

Comparative studies of Menactra versus Menomune showed that the two vaccines were comparable in terms of percentage of subjects achieving a 4-fold rise in Rabbit Complement SBA (rSBA).

Given these results, we assume that for each serogroup the percentage of subjects with hSBA seroresponse is 0%, 5%, or 10% higher in the MenACWY group compared to the Menactra group. Table 6.9.2-2 below shows, for each serogroup, the number of subjects that need to be tested by hSBA in order to have a 90% power to demonstrate non-inferiority for each of the four serogroups.

Table 6.9.2-2: Number of Subjects to be Tested by hSBA for 90% Power to Demonstrate Non-inferiority for Serogroups A,C,W and Y, Given Estimated Percentages of Subjects with Seroresponse in hSBA in MenACWY and Menactra groups

Serogroup	Percent of subjects with Seroresponse in hSBA MenACWY group (Group I)	Percent of subjects with Seroresponse in hSBA Menactra group (Group II)	Number of subjects evaluated in each group in order to have 90% power
A	75%	75%	395
	80%	75%	163
	80%	70%	98
	81%	76%	158
C	70%	70%	442
	75%	70%	186
	75%	65%	110
	80%	80%	337
W, Y	80%	80%	337
	85%	80%	135
	85%	75%	93
	85%	85%	268
	86%	81%	129

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Note: Non-inferiority is declared when the 95% CI is entirely to the right of –10%. Statistical superiority is declared when the 95% CI is entirely to the right of 0%.

Table 6.9.2-3 below shows the power for several sample sizes to demonstrate non-inferiority for serogroups A, C, W, Y given estimated percentages of subjects with seroresponse in hSBA in the MenACWY and Menactra groups.

Table 6.9.2-3: Sample Sizes in the MenACWY and Menactra Groups to Demonstrate Non-Inferiority with High Power for Serogroups A, C, W, Y Given Estimated Percentage of Subjects with hSBA Seroresponse

	MenACWY Group		Menactra Group		
Serogroup	Percentage with Seroresponse in hSBA	N / Group	Percentage with Seroresponse in hSBA	N / Group	Power for Non-Inferiority
A	70%	170	75%	170	56%
	80%	170	75%	170	91%
	80%	170	70%	170	99%
	81%	170	76%	170	92%
C	70%	170	70%	170	52%
	75%	170	70%	170	87%
	75%	170	65%	170	98%
	80%	170	80%	170	63%
W, Y	80%	170	80%	170	63%
	85%	170	80%	170	95%
	85%	170	75%	170	99%
	85%	170	85%	170	73%
	86%	170	81%	170	96%

(b) (4) version (b) (4) was used to perform the calculations, one sided α=0.025)

Again, we assume that, for each serogroup, the percentage of subjects in the 19 to 55 yoa adult group with hSBA seroresponse is 5% higher in the MenACWY group compared to Menactra. From Table 6.9.2-3 above, with 170 evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity primary objective and demonstrate non-inferiority is non-inferiority is 92%, 87%, 95% and 96% for serogroup A, C, W, and Y respectively. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority is equal to 73%.

Employing the serum bactericidal activity geometric mean titer response using human complement (hSBA GMTs), immunogenicity of the MenACWY group will be considered non-inferior to the immunogenicity of the Menactra group if the lower limit of the two-sided 95% confidence interval of the ratio of the MenACWY to Menactra GMTs, as measured by hSBA is $\geq$0.5 at one month after vaccination, when administered to healthy subjects 19 to 55 years of age. The within group standard deviation for the log10 hSBA titers was assumed equal to 0.73 for

serogroup A, 1.06 for serogroup C, 0.65 for serogroup W, and 0.80 for serogroup Y. These estimates were obtained, respectively, as the square root of the upper limit of the 80% CI of the within group variance observed for each serogroup in the previous Novartis MenACWY V59P6 study.

Table 6.9.20-4 below shows the power to demonstrate non-inferiority for this secondary objective for each serogroup using the standard deviations for each serogroup, highest:lowest GMT ratio, and sample sizes determined above for testing the primary null hypothesis.

Table 6.9.2-4: Power Calculations for Showing Non-Inferiority of MenACWY to Menactra Using the Lower Limit of the Two-Sided 95% CI on the ratio of the MenACWY to Menactra hSBA GMTs for Each Serogroup and Selected Group Sizes from Table 8

Serogroup	Highest:Lowest GMT Ratio	MenACWY N Per Group	Menactra N Per Group	Power for Non-Inferiority
A	1.0	170	170	96%
	1.2	170	170	79%
C	1.0	170	170	74%
	1.2	170	170	48%
W	1.0	170	170	98%
	1.2	170	170	88%
Y	1.0	170	170	93%
	1.2	170	170	72%

With 170 evaluable subjects assayed for serogroup A, C, W and Y in each of the two groups, the power to reject the null hypothesis associated with the non-inferiority immunogenicity secondary objective for hSBA GMTs and demonstrate non-inferiority is 96%, 74%, 98%, 93% for A, C, W, and Y, respectively, assuming a true underlying highest: lowest GMT ratio of 1. Assuming the results for the four serogroups are independent, the overall power to demonstrate immunologic non-inferiority using hSBA GMTs is equal to 75%.

Safety

The primary safety null hypothesis is that the upper limit of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination between the MenACWY and Menactra groups ($p_{MenACWY} - p_{Menactra}$) is ≥ 6%. Table 6.9.2-5 below shows the power to demonstrate non-inferiority for safety for different percentages of subjects experiencing at least one severe - systemic reaction during the first 7 days after vaccination.

Table 6.9.2-5: Power to Demonstrate Non-Inferiority for Safety for Different Percentages of Subjects Experiencing At Least One Severe Systemic Reaction During the First 7 Days after Vaccination

Percentages of Subjects Experiencing At Least One Severe Systemic Reaction		
MenACWY Group N=1900	Menactra Group N=900	Power for Non-Inferiority
2%	2%	99%
3%	3%	99%
4%	4%	98%
5%	5%	97%

Assuming a sample size of 1900 subjects in the MenACWY group (Group I) and 900 subjects in the Menactra group (Groups II) and percentage of subjects experiencing at least one severe systemic reaction equal to 5% in both groups, the power to demonstrate non-inferiority for safety is equal to 99% (one sided α=0.025). From a perspective of detecting uncommon local or systemic reactions, or AEs, Table 6.9.2-6 (below) gives the probabilities of observing at least one subject with one such event for either vaccine group for several underlying event rates.

Table 6.9.2-6: Probability of Observing At Least One Subject with an Uncommon Event in the MenACWY and Menactra Groups for Given Underlying Event Rates

Underlying Event Rate	Probability of observing at least one event in Group I (MenACWY) N=1900	Probability of observing at least one event in Group II (Menactra) N=900
1/100	>99.9%	>99.9%
1/200	>99.9%	98.9%
1/500	97.8%	83.5%
1/1000	85.0%	59.3%

6.10 Documentation of Study Findings

The sponsor will supply a set of CRF collations. The CRFs do not require carbon paper. The investigator must retain the bottom copy, and all other copies will be returned as directed by the sponsor. Instructions on how to complete these forms will be given to the investigator.

The investigator who will sign and date the CRFs must enter all study data. If the investigator authorizes other persons to make entries on the CRF, the names, positions, signatures and initials of these persons must be supplied to the sponsor (e.g. a sub investigator might join the study after the site initiation visit and be authorized by the investigator to sign the CRFs).

All entries in the CRFs must be made *legibly* in black ball-point pen (*not pencil, felt tip or fountain pen*).

No data will be reported directly on the CRFs without source documentation.

Details regarding the percentage of CRFs verified by source documentation by the Study Monitor will be included in the V59P17 Monitoring Plan.

For each enrolled subject a CRF collation must be signed and dated by the investigator named in the study protocol or on the FDA 1572 form. CRFs must be completed during/after each study visit. Arrangements will be made by the monitor to collect the CRFs on completion. No CRFs are to be mailed to the sponsor without specific authorization.

The investigator must give a reasonable explanation for all missing data.

If corrections are made to entries in the CRF by the investigator or designee, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made after review and signature by the investigator, he/she must confirm and endorse the changes by signing and dating the study termination CRF again.

As part of the conduct of the trial, Novartis Vaccines may have questions about the case report form data after the CRFs are collected from the site. These questions will be documented using Data Clarification Forms (DCFs). Novartis Vaccines will answer the question if the answer is self-evident on "internal" DCFs, but the investigator will need to review these changes. If the query is not self-evident, Novartis Vaccines will ask the investigator to provide the answer on an "external" DCF and sign it. Novartis Vaccines will send the investigator a copy of each completed internal DCF. The investigator will review them and if he/she disagrees with the resolution, he/she will notify the site monitor, who will then generate a new DCF documenting the investigator's correction. The investigator will be requested to file each of the DCFs (both levels) for the trial.

Definitions of the DCF types are as follows:

Internal DCF: A query for which the resolution is self-evident. It can be answered without changing the meaning of the data (such as moving data from one box to another) or using logical numeric flow (for example, if an adverse event number is missing, the next number in sequence can be assigned). Internal corrections are defined in either the assumptions for internal queries guideline or in study-specific assumptions. The Clinical Data Coordinator or the Clinical Research Associate can answer an internal query. Key safety (e.g. adverse event relationship) or primary endpoint data queries are not to be handled as an internal DCF.

External DCF: A query that requires information from the investigator. Key safety (e.g. adverse event relationship) or primary endpoint data queries must be handled as an external DCF.

6.11 Record Retention

Investigators must retain all study records required by Novartis Vaccines and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis Vaccines representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

6.12 Use of Information and Publication

Novartis Vaccines and Diagnostics recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement.

7. REFERENCE LIST

1. Andersen BM. Mortality in meningococcal infections. Scand J Infect Dis 1978;10:277-82.
2. De Wals P, Hertoghe L, Reginster G, Borlee I, Bouckaert A, Dachy A, et al. Mortality in meningococcal disease in Belgium. J Infect 1984;8(3):264-73.
3. Halstensen A, Pedersen SH, Haneberg B, Bjorvatn B, Solberg CO. Case fatality of meningococcal disease in western Norway. Scand J Infect Dis 1987;19(1):35-42.
4. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81(4):536-8.
5. Campagne G, Chippaux JP, Djibo S, Issa O, Garba A. [Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger)]. Bull Soc Pathol Exot 1999;92(2):118-22.
6. Centers for Disease Control and Prevention. Laboratory-based surveillance for meningococcal disease in selected areas--United States, 1989-1991. Morbidity Mortality Weekly Report (MMWR); CDC Surveillance Summaries 1993;42 (SS-2):21-30.
7. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Carter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894-1901.
8. Ramsay M, Kaczmarski E, Rush M, Mallard R, Farrington P, White J. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev 1997;7(4):R49-54.
9. Decosas J, Koama JB. Chronicle of an outbreak foretold: meningococcal meningitis W135 in Burkina Faso. Lancet Infect Dis 2002;2(12):763-5.
10. Taha M-K, Bichier E, Perrocheau A, Alonso J-M. Circumvention of herd immunity during an outbreak of meningococcal disease could be correlated to escape mutation in the *porA* gene of *Neisseria meningitidis*. Infect Immun 2001;69(3):1971-1973.
11. du Chatelet IP, Alonso JM, Taha MK. [Clonal expansion of *Neisseria meningitidis* W135. Epidemiological implications for the African meningitis belt]. Bull Soc Pathol Exot 2002;95(5):323-4; discussion 324-5.
12. Rosenstein N, Fischer M, Tappero JW. Meningococcal Vaccines. Infectious Disease Clinics of North America 2001;15(1):155-169.
13. Centers for Disease Control and Prevention. Meningococcal disease and college students: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2000;49(RR-7):13-20.
14. Cadoz M, Armand J, Arminjon F, Gire R, Lafaix C. Tetravalent (A, C, Y, W 135) meningococcal vaccine in children: immunogenicity and safety. Vaccine 1985;3(3):340-342.
15. King WJ, MacDonald NE, Wells G, Huang J, Allen U, Chan F, et al. Total and functional antibody response to a quadrivalent meningococcal polysaccharide vaccine among children. Journal of Pediatrics 1996;128(2):196-202.
16. Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. Pediatrics 1977;60(5):673-680.

17. Reingold AL, Hightower AW, Bolan GA, Jones EE, Tiendrebeogo H, Broome CV, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet 1985;2(July 20, 1985):114-118.
18. Käyhty H, Mäkelä PH, Peltola H. Immunological basis for PRP vaccines. In: Ellis RW, Granoff DM, editors. Development and Clinical Uses of Haemophilus b Conjugate Vaccines. New York, NY: Marcel Dekker Inc.; 1994. p. 1-18.
19. Rosenstein N, Perkins B. Update on *Haemophilus influenzae* serotype b and meningococcal vaccines. Pediatr Clin North Am 2000;47(2):337-352, vi.

8. SIGNATURE PAGE

SIGNATURE PAGE:

Study title: A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and An Open-Label Study to Evaluate the Safety and Immune Response to Novartis Meningococcal ACWY Conjugate Vaccine and Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) in Healthy Subjects 56-65 Years of Age

Study Number: V59P17

I have read the foregoing protocol and agree to conduct the clinical trial as outlined. I agree to conduct the trial in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____

Investigator Signature Date

Print name:_____

On behalf of Novartis Vaccines & Diagnostics, Inc., I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical trial.

_____ _____

Medical Monitor Signature Date

Print name:_____

APPENDIX A: LIST OF CENTRAL LABORATORIES

The SBA analyses will be performed at:

Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany

Tel. +49 (0)6421-39-3439/3712
Fax. +49 (0)6421-39-5826

Other laboratories may be employed, as directed by the sponsor.

APPENDIX B: SHIPPING AND HANDLING OF LABORATORY SPECIMENS (PLEASE REFER TO STUDY MANUAL FOR DETAILS)

1. Blood must be centrifuged, separated and frozen as soon as possible after collection. Make sure that coagulation is complete before separating the serum from blood components.

2. Please use the cryotubes provided. Be aware that the maximum-fill volume for these tubes is 90 % of rated capacity, i.e., 3.6 mL, to allow for expansion of the frozen serum. The tubes are marked with a maximum-fill line. Other sizes of cryotubes are not acceptable; if you have an inadequate supply, please contact your Monitor and additional tubes will be provided.

3. Close the tubes before freezing, and check to make sure that the caps are completely tight before packing for shipment.

4. Barcode labels are to be placed lengthwise down the tubes (not wrapped around). Barcodes are machine-readable only when their entire length runs along a flat surface. Please do not write on, make markings through, or otherwise deface the barcode. Make sure that labels are securely attached so that they do not pull away from the tubes after freezing. It is not necessary to fasten the label to the tube with adhesive tape.

5. Before the start of the trial, prepare separate cryoboxes for original and duplicate samples ("Original" and "Duplicate" labeled cryotubes). After blood has been collected, centrifuged and separated, place labeled tubes in the respective labeled cryoboxes "Original" and "Duplicate". Keep the tubes in numerical order by subject number.

6. Freeze tubes at ≤ -18 °C (+/- 6°C) in an upright position so that serum does not come into contact with the cap. Tubes may be stored in any convenient position once they are frozen. Do not "quick-freeze" tubes by immersing them in either dry ice or liquid nitrogen; this may crack the tubes.

7. Pack cryotubes for shipment according to the instructions provided. If you have questions, please contact your Monitor.

8. Pack the original shipping log in an envelope inside the cardboard shipping box, on top of the Styrofoam insulated shipper. Fax the shipping log to:

Dr. Annette Karsten
Novartis Vaccines & Diagnostics
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Tel. +49 (0)6421-39-3439/3712
Fax. +49 (0)6421-39-5826

9. Duplicate samples should be sent still frozen after confirming the first shipment arrived safely.

APPENDIX C: SEROLOGY PROCEDURES

Retention of Study Records

The raw data, test records, and other laboratory documents generated during the course of the study will be retained in Clinical Serology, Novartis Vaccines, Marburg for 15 years

Quality Assurance Reviews

Quality Assurance of operations that are routinely performed may be carried out by means of process-based inspections. Technical review on all recorded stages of the assay data will be performed.

Objectives

To test human sera for the presence of bactericidal antibodies to:
N. meningitidis serogroups Men A, Men C, Men W-135, Men Y

Sample Storage

Frozen serum samples will be logged and stored at a temperature of minus 18°C ± 6°C in Clinical Serology, Novartis Vaccines, Marburg.

Test Methods and Procedures

Assay name: MenA-BCA
Antigen: *Neisseria meningitidis* serogroup A (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenC-BCA
Antigen: *Neisseria meningitidis* serogroup C (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenW-135-BCA
Antigen: *Neisseria meningitidis* serogroup W-135 (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Assay name: MenY-BCA
Antigen: *Neisseria meningitidis* serogroup Y (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none
Seroconversion/protection limit: not defined

Equipment

Equipment as listed in the relevant Clinical Serology, SOP and associated documents.

Procedures

All procedures will be carried out according to the relevant SOPs and associated documents from Clinical Serology Marburg, Novartis Vaccines.

CLINICAL STUDY PROTOCOL V59P18

Original issued 21 May 2007
Amendment 1 issued 15 October 2007
Amendment 2 issued 11 March 2008

A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis Men ACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents

Version number 1 number IND 11278

SPONSOR	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 53100 Siena, Italy
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MEDICAL MONITOR:	Olga Mellone, MD Phone number: +55 11 5532 2465 E-mail: olga.mellone@novartis.com Mobile phone: + 55 11 8524 5555 Fax number: +55 11 55322466
STUDY MONITOR	Caroline Tonussi Phone number: + 55 11 5532 2461 E-mail: caroline.tonussi@novartis.com

For trial related **emergencies out of office hours** please contact: +49 (0) 151 12641663

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May not be used, divulged, published or otherwise disclosed without written consent of Novartis Vaccines.

STUDY SYNOPSIS

A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents

INVESTIGATORS:

Principal Investigator: Adriano Arguedas, MD
Instituto de Atencion Pediatrica
Del Restaurante La Bastilla 100 mts Sur y 25 Oeste
San Jose, Costa Rica

STUDY CENTRE: Costa Rica

STUDY PERIOD
Approximately 11 months overall: 2 months of enrollment and up to 9 months of individual subject participation

CLINICAL PHASE:
Phase 3

RATIONALE:

Neisseria meningitidis causes life-threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified, with serogroups A, B, C, W135 and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. Licensed tetravalent polysaccharide vaccines against serogroup A, C, W135 and Y have been available for many years and are widely used. However they do not provide long-term protection and are poorly immunogenic, even in the short-term, in children below 2 years of age.

Based upon the recent, successful development of conjugate vaccines designed to prevent disease caused by *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* serogroup C, Novartis is developing a conjugate Men ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM197 (a non-toxic mutant of diphtheria toxin).

Novartis Men ACWY conjugate vaccine has already been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 3200

subjects (from infants up to 55 years old) have received at least one dose of the formulation of Novartis Men ACWY conjugate vaccine (MenACWY) being tested in this study.

A similar tetravalent meningococcal conjugate vaccine, Menactra is licensed and recommended in the United States for active immunization against invasive meningococcal disease in persons 11 to 55 years of age. In adolescents, a combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap) and a vaccine against Human Papillomavirus Recombinant Vaccine [Types 6, 11, 16, 18] (HPV) have also been recommended for routine use recently by ACIP.

Boostrix® (GlaxoSmithKline) is a tetanus, diphtheria, and acellular pertussis (Tdap) booster vaccine available for adolescents 10 through 18 years of age, licensed in the U.S. in 2005. During 2004, a total of 8,897 (34%) of the 25,827 reported pertussis cases in the U.S. occurred among adolescents aged 11–18 years (incidence for adolescents: ~30/100,000 population); 17 states each reported >100 pertussis cases in adolescents. The incidence of pertussis in adolescents varies widely among states and from year-to-year. During 2000-2004, a total of 11 states had an annual incidence of reported pertussis in adolescents of >50 per 100,000 population during at least 1 year.

GARDASIL® (Merck & Co., Inc.) was approved by the FDA in June 2006 and is indicated in girls and women 9-26 years of age for the prevention of cervical cancer, genital warts, and genital precancerous or dysplastic lesions caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18. GARDASIL protects recipients against 4 types of HPV, including the two types that cause most cervical cancers and the two types that cause the most genital warts. About 20 million people are infected with HPV in the United States and almost 3,700 women die of cervical cancer in the US each year. The ACIP recommends that GARDASIL be routinely given to girls when they are 11 or 12 years of age, before people become sexually active (i.e., before women are exposed to the viruses). GARDASIL can be administered as early as age 9 years, and can also be given to women 13 to 26 years old. GARDASIL is to be given as a three dose series completed over 6 months.

The main objective of the proposed phase 3 study is to describe and compare the safety and immunogenicity profile of a single dose of Novartis Men ACWY administered either concomitantly with the two licensed combined vaccines, Tdap (GlaxoSmithKline, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine, (Merck & Co., Inc., GARDASIL®) or alone to healthy adolescents 11-18 years of age. An important additional objective is to evaluate the safety of serial administration of two diphtheria-containing vaccines (e.g. MenACWY followed by Boostrix). Although both Boostrix and GARDASIL are licensed for younger ages, the lower limit of the age range (11 years) was selected for this study because of earlier decisions for definition of adolescent during the Novartis meningococcal vaccine development program.

A comprehensive and detailed review of investigational Novartis Men ACWY conjugate vaccine is contained in the Investigator's Brochure supplied by the Sponsor while for Boostrix and GARDASIL, please refer to the respective target product profiles.

OBJECTIVES:

Primary Immunogenicity Objectives and Measures

a. To demonstrate that the immune response of MenACWY vaccine when given concomitantly with Tdap and HPV vaccines is not inferior to MenACWY when given alone as directed against *N. meningitidis* serogroups A, C, W and Y following a single dose of vaccine. Response will be measured by serum bactericidal activity using human complement (hSBA) in terms of percentage of subjects with seroresponse, defined as hSBA ≥ 1:8 post vaccination if baseline hSBA < 1:4 or achieving a titer post vaccination of at least four times the subject's baseline titer if the subject's baseline titer is ≥ 1:4.

b. To demonstrate that the immune response of Tdap given concomitantly with MenACWY is not inferior to the response of Tdap given alone. Immunogenicity response of Tdap is defined as 1) percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL, anti-tetanus toxin ≥1.0 IU/mL and 2) anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), anti-pertactin (anti-PRN) geometric mean concentrations (GMC).

c. To demonstrate that the immune response to MenACWY administered alone one month after Tdap is not inferior to the immune response of MenACWY administered alone one month prior to Tdap as measured by seroresponse directed against *N. meningitidis* serogroups A, C, W, and Y.

Secondary Immunogenicity Objectives and Measures

a. To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is not inferior to the response when HPV is given alone. Immune response against HPV virus-like particles (VLPs) for types 6, 11, 16, and 18 following a third dose of the HPV vaccine will be measured by competitive Luminex immunoassay (cLIA) in terms of:

   - The anti-HPV seroconversion (SC), defined as negative for anti-HPV at baseline and anti-HPV greater or equal a HPV type-specific cutoff at one month after the third dose of the vaccine.
   - The geometric mean titers (GMTs) to HPV Types 6, 11, 16, 18 at one month after the third dose of the vaccine.

b. To compare the immune response to Tdap administered alone one month after MenACWY to the immune response of Tdap administered alone one month prior to MenACWY with immune response as previously defined for the primary Tdap endpoint.

c. To assess the immunogenicity of MenACWY as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA≥1:4 and hSBA ≥ 1:8, directed against *N. meningitidis* serogroups A, C, W and Y.

d. To assess the immunogenicity of Tdap administered alone or concomitant with MenACWY and HPV as measured by anti-diphtheria and anti-tetanus GMCs and the percentage of subjects with a four-fold rise in antibody over baseline for anti-PT, anti-FHA, and anti-PRN titer.

Safety Objectives and Measures

a. To describe and compare the safety profile following a single dose of MenACWY given alone one month after Tdap to the safety profile following a single dose of MenACWY given alone one month before Tdap vaccine.

b. To describe the safety profile following a single dose of MenACWY given alone or concomitantly with Tdap and HPV vaccine.

c. To describe and compare the safety profile following a HPV given alone to HPV given concomitantly with Tdap and MenACWY vaccine.

The measures of safety in this study will be local and systemic reactions, oral temperature, and other AEs. For more details refer to Table 2.

METHODS:

This is a phase 3, open-label, single center, randomized, controlled study in healthy subjects aged 11-18 years.

Subjects will be included in the study if in good health as judged by physical examination and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 1620 healthy subjects aged 11-18 years will be randomized in a 1:1:1 ratio to 3 groups as shown in Table 1. The randomization will be stratified by gender and age group (11-14 years of age, 15-18 years of age). Equal numbers of subjects in each age group are planned to be enrolled (810 subjects into each age stratum).

Table 1

	Month 0	Month 1	Month 2	Month 4	Month 6	Month 7	Month 8	Month 9
Group (N)	**Day 1 Visit 1**	**Day 31 Visit 2**	**Day 61 Visit 3**	**Day 121 Visit 4**	**Day 181 Visit 5**	**Day 211 Visit 6**	**Day 241 Visit 7**	**Day 271 Visit 8**
I (540)	Serology Men ACWY+ Tdap + HPV	Serology	HPV		HPV	Serology		
II (540)	Serology Men ACWY	Serology Tdap	Serology HPV	HPV			HPV	Serology
III (540)	Serology Tdap	Serology Men ACWY	Serology HPV	HPV			HPV	Serology
*All subjects will have a telephone call 6 months after final MenACWY study immunization, if the subject terminates early from treatment								

A medical history will be obtained and an initial physical exam will be performed to establish eligibility. Blood samples (20 mL) for serological evaluations will be collected in all subjects at Visit 1 (Day 1) prior to administration of study vaccines, at one month after the first immunization (in all study groups), at one month after the second immunization (for group II and III) and at one month after the third HPV immunization (group I-III).

At Visit 1, the investigator, or a qualified person designated by the investigator, should fully inform the subject and his/her parent(s) or guardian(s), when applicable, of all pertinent aspects of the trial and the subject's consent or assent and his/her parent(s)/legal guardian's written informed consent will be obtained after which, subjects will be assigned a screening number. A medical history will be obtained and an initial physical exam will be performed to establish eligibility. A urine pregnancy test will be performed on all females regardless of childbearing potential. Pregnancy tests will be performed at each visit where immunizations are given, prior to each immunization and at the last study visit. If the subjects are in good health, according to the clinical judgment of the investigator, and they meet all inclusion criteria and no exclusion criteria, they may be enrolled in the study. Enrolled subjects will be identified by a subject number.

After providing a blood sample, subjects will be immunized according to a randomization list. The vaccines will be administered intramuscularly (IM) in the deltoid muscle: Men

ACWY vaccine will be administered in the deltoid region of the right arm, Tdap in the deltoid region of the left arm and HPV vaccine in the upper anterolateral region of the thigh. The subjects will remain in the clinic for 30 minutes following immunization to assess for immediate reactions. During Visit 1, subjects and subjects' parents/legal guardians, where applicable, will be instructed on how to measure oral temperature. In addition, subjects and the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a diary card. The diary cards will be collected during the subsequent site visit and a new diary card will be issued. Similar procedures will be followed after each study injection (e.g., after the second and third HPV immunizations).

Subjects, parents or legal guardians will receive a phone call 2 days after each study immunization to query for SAEs and anything of concern to the subject, parent or guardian. If a telephone call is not possible a clinic or home visit may be performed instead. In addition subjects will be queried about significant arm swelling. If significant arm swelling is reported at that time (or any time prior to the next study visit), the subject should be evaluated by study personnel. All events of arm swelling will be recorded on the Adverse Events CRF page, with a comment on the Comments CRF page to detail the event. At this phone call the study staff will answer any questions the subject, parent or guardian may have about diary card completion. The subject, parent or guardian will be reminded of which AEs and concomitant medications to record for the appropriate interval and will remind the subject/parent or guardian of the next scheduled visit.

Medically significant AEs (ER visits and hospitalizations) and all SAEs will be collected for all subjects for the duration of the study. The subjects and/or the subjects' parents/legal guardians, where applicable, will be instructed on how to record medically significant AEs, SAEs, and medications taken as detailed in Table 2.

Subjects will be followed for safety until 30 days after their last vaccination or for 6 months after the last MenACWY immunization, whichever occurs later. This applies also to subjects who terminate early from the study (see Table 2). For subjects who terminate early from the study, before completing a 6 month follow up interval after their last MenACWY injection, a worksheet will be completed for this interval to aid subjects, parents/legal guardians in recollection of events and medications. This worksheet will not be collected and will not be given to subjects who have completed a 6-month safety follow up after MenACWY administration on study.

Table 2

Medical History: Significant past diagnoses including allergies, hospitalizations, major surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine will be collected	From birth
Immunization History: Immunization history will be collected in subject source. Only diphtheria containing vaccines will be collected in the subject CRF.	From birth
Immediate reactions: Signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 minutes after each immunization
Stayed home due to reaction?	For 7 days after each immunization
Antipyretics/Analgesics used?	For 7 days after each immunization
Temperature: Oral temperature	For 7 days after each immunization
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days after each immunization
Systemic reactions: Chills, nausea, malaise, myalgia, arthralgia, headache, and rash *If persisting beyond Day 7 will be reported as an AE*	For 7 days after each immunization
All Adverse Events	For 7 days after each immunization
Adverse Events: AEs that require a medical office visit, consultation and/or results in premature withdrawal from the study.	From Visit 1 through 30 days after last immunization

Medically significant AEs: **AEs requiring Emergency Department visit, or leading to a subject's withdrawal, or hospitalizations** with the exclusion of pre-planned medical office visits or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis **(Note, the excluded conditions above will NOT be collected or recorded in CRFs.)**	Throughout the study including 6-month follow up period for subjects who terminate early
Serious Adverse Events: A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: • results in death • is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred) • requires or prolongs inpatient hospitalization • results in persistent or significant disability/incapacity • results in a congenital anomaly/birth defect • requires intervention to prevent permanent impairment or damage • is an <u>important and significant medical event</u> that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. *All SAEs will be monitored until resolution and/or the cause is identified.* *If an SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	Throughout the study
Medications: All prescription and non-prescription medications (with the exception of mineral supplements and vitamins).	For 7 days after each immunization
Prescription medications	From Visit 1 through 30 days after last immunization
Prescription medication taken for medically significant AEs (see medically significant AEs above).	From 30 days after last immunization or through 6-month study follow up phone call for subjects

	who terminate early

NUMBER OF SUBJECTS PLANNED:

Approximately 1620 11-18 year old subjects (540 for each immunization group), will be enrolled. The randomization will be stratified by gender and age group (11-14 years of age, 15-18 years of age). Equal numbers of subjects in each age group are planned to be enrolled (810 subjects into each age stratum).

SUBJECTS CHARACTERISTICS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Healthy subjects 11-18 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are female and male subjects who have shown to be healthy at screening and who are:

1. 11-18 years of age inclusive who have given their written consent/assent and if applicable, whose parents or legal guardians have given written informed consent at the time of enrollment;
2. virgins (both male and female) with no intention of becoming sexually active during the study period;
3. available for all visits and telephone calls scheduled for the study;
4. in good health as determined by:

medical history
physical assessment
clinical judgment of the investigator

5. who have been properly vaccinated against diphtheria, tetanus, pertussis (i.e., who have received five doses of pediatric DTP/DTaP before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed);

Informed consent must be obtained for all the subjects before enrollment into the study.

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling to give their written assent / consent ;
2. who and/or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;

3. who have a positive pregnancy test;
4. who had a previous confirmed or suspected disease caused by *N. meningitidis*;
5. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
6. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational). (Exception: Receipt of OMP-containing Hib vaccines is permitted);
7. who have received prior human papillomavirus (HPV) vaccine;
8. who have received investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to completion of the study;
9. who have received licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated during the study period (Exception: Inactivated influenza vaccine may be administered up to 15 days prior to study immunization and no less than 15 days after study immunization);
10. who have received a live viral vaccine within 21 days prior to enrollment;
11. who have experienced, within the 7 days prior to enrollment, significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (defined as body temperature $\geq$ 38°C) within 3 days prior to enrollment;
12. who have any serious acute, chronic or progressive disease such as
    a. history of cancer
    b. complicated diabetes mellitus
    c. advanced arteriosclerotic disease
    d. autoimmune disease
    e. HIV infection or AIDS
    f. blood dyscrasias
    g. congestive heart failure
    h. renal failure
    i. severe malnutrition

(Note: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment)

13. who have epilepsy, any progressive neurological disease or history of Guillain-Barre syndrome;
14. who have a history of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;

15. who have a condition that is a contraindication to vaccination as indicated in the most recent package inserts (including latex allergy);
16. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):

- receipt of immunosuppressive therapy within 30 days prior to enrollment (systemic corticosteroids administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
- receipt of immunostimulants
- receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 90 days prior to enrollment and for the full length of the study

17. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
18. who have Down's syndrome or other known cytogenic disorders;
19. who and/or whose families are planning to leave the area of the study site before the end of the study period;
20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Reasons for delaying subsequent immunizations

I. Significant acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy commenced within the past 7 days;

II. Oral temperature of ≥ 38.0°C or presence of an acute systemic illness on the day of immunization;

III. Use of systemic corticosteroids (oral, intramuscular or intravenous) administered for more than 5 days or in a daily dose >1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 15 days;

IV. Use of systemic corticosteroids (oral, intramuscular or intravenous) administered during the study in a daily dose <1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 7 days;

V. Any other licensed vaccines can be administered up to 30 days prior to study immunization and no less than 30 days after the study immunization.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore a blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

TEST VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

Men ACWY conjugate vaccine

The investigational Novartis Men ACWY vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the liquid Men CWY component. The Men ACWY vaccine will be administered IM in the deltoid region of the right arm.

After reconstitution the Men ACWY vaccine will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA, (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC, (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY (b) (4) µg CRM_{197}
Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

HPV vaccine (Merck & Co., Inc. GARDASIL®)

Composition	Quantity per 0.5 mL dose
HPV 6 L1 protein	20 mcg
HPV 11 L1 protein	40 mcg
HPV 16 L1 protein	40 mcg
HPV 18 L1 protein	20 mcg

Other ingredients:

Amorphous aluminum hydroxyphosphate sulphate adjuvant (225 micrograms Al). Sodium chloride, L-histidine, Polysorbate 80, Sodium borate, Water for Injections.

One 0.5 mL dose of GARDASIL® vaccine will be administered IM in the upper anterolateral area of the thigh.

Tdap vaccine (BOOSTRIX®)

Licensed combined Tdap vaccine Boostrix® (manufactured by GSK Biologicals, Rixensart, Belgium) is supplied as a 0.5 mL dose.

Composition	Quantity per 0.5 mL dose
tetanus toxoid (T)	5 Lf
diphtheria toxoid (d)	2.5 Lf
Inactivated PT	8 µg
filamentous hemagglutinin (FHA)	8 µg
pertactin (PRN)	2.5 µg

Other ingredients:

NaCl (4.5 mg), aluminum adjuvant (not more than 0.39 mg aluminum by assay), ≤ 100 mcg of residual formaldehyde, and ≤ 100 mcg of polysorbate 80 (Tween 80).

One 0.5 mL dose of Boostrix® vaccine will be administered IM in the deltoid area of the left arm.

CONCOMITANT VACCINES:

No additional concomitant vaccines other than those planned in the study will be administered as a part of the study. No other licensed vaccines should be administered within 30 days of any study immunization.

Inactivated influenza vaccine may be administered up to 15 days prior to study immunization and no less than 15 days after study immunization. This immunization will be reported as a concomitant medications in the subject's CRF.

MEASURES OF IMMUNOGENICITY:

The immune response one month after primary vaccination to *B. pertussis*, diphtheria and tetanus toxoid will be measured by ELISA. Immune response against HPV VLPs for types 6, 11, 16, and 18 will be measured by cLIA.

The ability of MenACWY to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (hSBA) will be measured.

Additional analyses to further characterize the immune response to the vaccine components may be performed (e.g., SBA using rabbit complement).

MEASURES OF SAFETY:

Measures of safety and reactogenicity include data from observed local reactions (i.e., tenderness, erythema, and induration) and systemic reactions (i.e., chills, nausea, malaise, myalgia, arthralgia, headache, and rash). For all subjects, these data will be collected together with oral temperature, analgesic / antipyretic medication use and all adverse events during the first 7 days after each study vaccine injection. SAEs and AEs necessitating a medical office or ER visit and/or resulting in premature withdrawal of subjects from the study will be collected and recorded by study personnel during each of the study visits.

SEROLOGY:

hSBA analyses will be performed at:
Novartis Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany
Phone: +49 (0) 6421 39 3439/3712

Tdap ELISA testing will be performed at:
(b) (4)

HPV testing will be performed at (b) (4)

Other laboratories may be employed, as directed by the sponsor.

CRITERIA FOR ASSESSING IMMUNOGENICITY OBJECTIVES:

Primary:

The immunogenicity of MenACWY given concomitantly with HPV and Tdap will be considered non-inferior to the immunogenicity of MenACWY administered alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at 1 month after MenACWY vaccination {$P_{MenACWY+HPV+Tdap}$ minus $P_{MenACWY}$} is greater than -10% for each serogroup (Group I vs. Group II at visit 2). Seroresponse is defined as hSBA $\geq$ 1:8 post vaccination if baseline hSBA < 1:4 or a titer post vaccination of at least four times the subject's baseline titer if the subject's baseline titer is $\geq$ 1:4.

The comparison of the immunogenicity of Tdap given concomitantly with MenACWY to the response of Tdap given alone will be assessed by examining:

- the percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL and anti-tetanus toxin ≥1.0 IU/mL. Tdap concomitant with MenACWY will be considered non-inferior to Tdap alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects {$P_{MenACWY+HPV+Tdap}$ minus P_{Tdap}} is greater than -10% for each antigen (Group I vs. Group III at visit 2).

- the ratios of anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), anti-pertactin (anti-PRN) geometric mean concentrations (GMC). Tdap concomitant with MenACWY will be considered non-inferior to Tdap alone if, for PT, FHA, and pertactin, the lower limit of the two-sided 95% CI for the ratio of the GMCs ($GMC_{MenACWY + Tdap}$ / GMC_{Tdap}) at 1 month after vaccination is > 0.67 (GMC of Group I/GMC of Group III at visit 2).

The immunogenicity of MenACWY given after Tdap will be considered non-inferior to the immunogenicity of MenACWY administered alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at 1 month after MenACWY vaccination {$P_{MenACWY\ after\ Tdap}$ minus $P_{MenACWY}$} is greater than -10% for each serogroup (Group II at visit 2 vs. Group III at visit 3).

The success criteria for this study is a composite based upon the three co-primary objectives: a demonstration of noninterference of concomitant HPV and Tdap with MenACWY response, a demonstration of the noninterference of serial Tdap-MenACWY administration on MenACWY response, and a demonstration of noninterference of concomitant HPV and MenACWY with Tdap response. This study will be considered a success if, for each MenACWY serogroup, MenACWY concomitant with HPV and Tdap is shown to be non-inferior to MenACWY alone, MenACWY given after Tdap is shown to be non-inferior to MenACWY alone, and, for each Tdap component, Tdap concomitant with HPV and MenACWY is shown to be non-inferior to Tdap alone.

Secondary:

MenACWY serum bactericidal activity will be measured for each serogroup at the relevant timepoints and expressed as GMTs, percent of subjects with hSBA ≥ 1:4, hSBA ≥ 1:8, and seroresponse.

The immune response one month after primary vaccination to *B. pertussis*, diphtheria and tetanus toxoid will be measured by ELISA. Immune response against HPV VLPs for types 6, 11, 16, and 18 will be measured by cLIA. GMC/GMTs and response rates at the relevant points will also be calculated for the antigens in Tdap and HPV vaccine.

Immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV given alone if the lower limit of the two-sided 95% CI for the

difference in the percentage of subjects with anti-HPV seroconversion (SC), at 1 month after the third dose of the HPV vaccine {$P_{HPV + MenACWY}$ minus P_{HPV}} is greater than -5%. Anti-HPV SC is defined for those subjects negative for anti-HPV at baseline, an anti-HPV ≥ HPV type-specific cutoff after vaccination (see Appendix C for HPV-type specific cut-off values). In a separate analysis comparing the immune response of HPV concomitant with MenACWY to HPV alone, the ratio of GMTs will be assessed to determine non-inferiority. The immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV alone if the lower limit of the two-sided 95% CI of the ratio of the GMTs ($GMT_{MenACWY+HPV}$ / GMT_{HPV}) is > 0.50 at 1 month after the third HPV vaccination for each HPV type. Treatment Groups II and III will be combined for the comparison to Group I in the HPV analyses. The success criteria for establishing non-interference of MenACWY on HPV immunogenicity requires that all eight HPV analysis (SC for the 4 HPV types, and GMT ratio for the 4 HPV types) meet the non-inferiority criteria.

The secondary examination of the interference of MenACWY on the Tdap response will compare the response after serial administration of MenACWY either before or after Tdap and be assessed using the same endpoints as previously described for the primary Tdap non-inferiority criteria (DT: percentage response, pertussis antigen: GMC ratio) (Group II at visit 3 vs Group III at visit 2).

CRITERIA FOR ASSESSING SAFETY OBJECTIVES:

Number of subjects with reported local and systemic reactions as well as number of subjects with reported serious adverse events and/or all adverse events up to day 7 and/or medically significant adverse events, will be calculated per immunization group.

STATISTICAL HYPOTHESIS:

Primary:

a. The null hypothesis associated with the primary ACWY immunogenicity objective is that for at least one serogroup, the seroresponse percentage in Group I is at least 10% lower than that in Group II at visit 2 (lower limit of the 95% CI of the difference in response rates is ≤ –10%).

b. The null hypothesis associated with the primary Tdap immunogenicity objective is that for either diphtheria or tetanus toxin, the percentage of subjects responding in Group I is at least 10% lower than that in Group III at visit 2 (lower limit of the 95% CI of the difference in response rates is ≤ –10%).

c. The null hypothesis associated with the primary pertussis non-inferiority objective is that for either PT, FHA, or pertactin, the lower limit of the two-sided 95% CI for the ratio of the GMCs ($GMC_{MenACWY + Tdap}$ / GMC_{Tdap}) at 1 month after vaccination is ≤ 0.67 (GMC of Group I/GMC of Group III at visit 2).

d. The null hypothesis associated with the second primary ACWY immunogenicity objective is that for at least one serogroup, the seroresponse percentage in Group III at visit 3 is at least 10% lower than that in Group II at visit 2 (lower limit of the 95% CI of the difference in response rates is $\leq -10\%$).

Secondary:

a. The null hypothesis associated with the HPV GMT non-inferiority objective is that for at least one of the four HPV types in GARDASIL, the lower limit of the two-sided 95% CI for the ratio of the GMTs ($GMT_{MenACWY + HPV} / GMT_{HPV}$) at 1 month after the third vaccination is ≤ 0.50 (GMT of Group I at visit 6/GMT of Group II+Group III at visit 8).

b. The null hypothesis associated with the HPV response objectives is that, for any of the HPV types, the lower limit of the two-sided 95% CI for the difference between the groups ($P_{MenACWY+HPV}$ minus P_{HPV}) in the percentage of subjects with antibody response greater than or equal to the HPV-type specific cut-off level at 1 month after the third dose is $\leq$ -5%.

c. The null hypothesis associated with the secondary Tdap immunogenicity objective is that for either diphtheria or tetanus toxin, the percentage of subjects responding in Group II at visit 3 is at least 10% lower than that in Group III at visit 2 (lower limit of the 95% CI of the difference in response rates is $\leq -10\%$).

d. The null hypothesis associated with the secondary pertussis non-inferiority objective is that for either PT, FHA, or pertactin, the lower limit of the two-sided 95% CI for the ratio of the GMCs ($GMC_{MenACWY + Tdap} / GMC_{Tdap}$) at 1 month after vaccination is ≤ 0.67 (GMC of Group II at visit 3/GMC of Group III at visit 2).

STATISTICAL POWER CONSIDERATIONS:

Primary Immunogenicity Objectives:

MenACWY:

Based on the antibody response of adolescents in Novartis study V59P6 who received a single dose MenACWY vaccine, the percentage of subjects with seroresponse at 1 month after vaccination was 80.7%, 75.2%, 84.6%, and 86.1%, respectively, for serogroups A, C, W, and Y. Assuming the subjects in this study will have similar immune response (rates are rounded down to be conservative), the following table shows the power to demonstrate non-inferiority for a given serogroup in the percentage of subjects with seroresponse, based on various group sizes, a non-inferiority criterion of –10%, and equal true underlying percentages in each group.

Table 3: Power to Demonstrate Non-Inferiority in the Percentage of Subjects with Seroresponse, Based on Various Group Sizes, and Equal True Underlying Percentages

Serogroup	True Percentage	Power Based on N=450 per group	Power Based on N=500 per group
A	81%	96%	98%
C	75%	93%	95%
W	85%	98%	99%
Y	86%	99%	99%

With 450 subjects per group, the power for the four antigens combined is 87%. If 500 subjects in each group are evaluable, the power for the four combined antigens is increased to 91.8%. Two co-primary objectives are based on this same non-inferiority comparison. Therefore, the combined power for these two endpoints (MenACWY+HPV+Tdap vs. MenACWY alone and MenACWY after Tdap vs. MenACWY alone) is 84.3% for 500 evaluable subjects per group.

Tdap:

Using the ELISA GMC response, immunogenicity of Tdap given concomitantly with MenACWY will be considered non-inferior to Tdap given alone if the lower limit of the two-sided 95% CI of the ratio of the MenACWY+Tdap to Tdap alone GMCs is > 0.67 at 1 month following vaccination. Only the three pertussis antibody responses will be assessed in this manner. From data publicly available regarding the variance of the GMCs for the pertussis antibody response to Boostrix (FDA clinical review 3/15/2005), it was determined that within group standard deviation for the $\log_{10}$ ELISA titers for pertussis toxin, filamentous hemagglutinin, and pertactin were 0.401, 0.351, and 0.622, respectively. These estimates were obtained as the square root of the upper limit of the 80% CI of the within group variance. The following table displays the power for the non-inferiority comparison of the GMC ratio between MenACWY plus Tdap and Tdap administered alone.

Table 4: Power Calculations for Showing Non-Inferiority of Tdap concomitant with MenACWY to Tdap Alone Using a 0.67 Lower Limit of the Two-Sided 95% CI of the Ratio of GMCs of the Pertussis Response (pertussis, FHA, pertactin), Based on Various Group Sizes, and Ratio of Tdap+MenACWY:Tdap GMC

Antigen	GMC Ratio	Power N=450 per group	Power N=500 per group
PT (aP)	1.0	99	99
	0.83	94	96
FHA	1.0	99	99
	0.83	98	99
Pertactin	1.0	98	99

	0.83	62	67

Therefore, with 500 subjects per group, the power to demonstrate non-inferiority is 99%, 99%, and 99% for PT, FHA, and pertactin, respectively and an assumed 1.0 ratio.

For the diphtheria and tetanus toxin components of Tdap, immunogenicity response is defined as the percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL, anti-tetanus toxin ≥1.0 IU/mL. Based on the antibody response quoted in the Boostrix package insert, the percentage of subjects with anti-diphtheria toxin ≥ 1.0 IU/mL and anti-tetanus toxin ≥ 1.0 IU/mL at 1 month after vaccination was 97.3% and 99.3%, respectively. Assuming the subjects in this study will have similar immune response, the following table shows the power to demonstrate non-inferiority for a given toxin in the percentage of subjects with immune response, based on various group sizes, a non-inferiority criterion of –10%, and different true underlying percentages in each group.

Table 5: Power to Demonstrate Non-Inferiority in the Percentage of Subjects with Diphtheria and Tetanus Response, Based on Various Group Sizes, and Various True Underlying Percentages

Antigen	True Percent Tdap	True Percent Tdap+MenACWY	Power Based on N=450 per group	Power Based on N=500 per group
Diphtheria	97%	97%	99%	99%
	97%	92%	91%	94%
Tetanus	99%	99%	99%	99%
	99%	95%	99%	99%

Assuming equal true underlying percentages, a sample size of 450 subjects per group provides 99% power for both anti-diphtheria and anti-tetanus toxin. All subjects will be assayed for all Tdap antigens. Therefore, with 450 subjects evaluable for D, T, PT, FHA and pertactin, assuming equal true underlying percentage responders between the two vaccine groups or a GMC ratio of 1.0, the combined power for the Tdap primary endpoints is 94%. If 500 subjects will be evaluable for D, T, PT, FHA and pertactin then power is 95%.

The overall power of this study is based on a multiplication of the power for all three co-primary endpoints. Therefore, combined across the two sets of four MenACWY serogroups and five Tdap antigens, the overall power of the study is 80.1% with 500 evaluable subjects per group. It is estimated that approximately 8% of subjects will be unevaluable for the immunogenicity analyses. To account for this loss, 540 subjects per group will be randomized.

Secondary Immunogenicity Objectives:

Based on the cLIA GMT response, immunogenicity of GARDASIL given concomitantly with MenACWY will be considered non-inferior to GARDASIL given alone if the lower limit of the two-sided 95% CI of the ratio of the MenACWY+GARDASIL to GARDASIL alone GMTs is ≥ 0.50 at 1 month following the third GARDASIL vaccination. The within group standard deviation for the $\log_e$ cLIA titers is assumed to be 0.721 for HPV type 6, 0.881 for HPV type 11, 1.124 for HPV type 16, and 1.090 for HPV type 18. These estimates were based on the square root of the upper limit of the 80% CI of the within group variance observed for each HPV type in the GARDASIL package insert. The following table displays the sample size necessary to achieve 99% power for the non-inferiority comparison of GMT ratio between MenACWY plus GARDASIL and GARDASIL administered alone.

Table 6: Sample size Calculations Necessary for 99% Power to Show Non-Inferiority of MenACWY concomitant with GARDASIL to GARDASIL Alone Using a 0.50 Lower Limit of the Two-Sided 95% CI of the Ratio of GMTs of the four HPV Types

HPV Type	GMT Ratio	Sample Size For 99% Power
6	1.0 0.83	41 75
11	1.0 0.83	61 111
16	1.0 0.83	98 179
18	1.0 0.83	92 169

As shown, with 100 subjects per group and a ratio of 1.0, the power for each non-inferiority comparison is >99%. Assuming a higher GMT response for the GARDASIL alone group, 200 subjects per group would provide greater than 99% power for each of the comparisons.

In terms of SC, the immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV given alone if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with anti-HPV seroconversion (SC), at 1 month after the third dose of the HPV vaccine $\{P_{HPV + MenACWY}$ minus $P_{HPV}\}$ is greater than -5%. When HPV vaccination is administered alone, the percentage of subjects with seroconversion at one month after the third dose of the HPV vaccine is very close to 100%. The table below shows, for various sample sizes, the power to reject the null hypothesis for each antigen.

Percent with HPV SC	Sample Size	Power
99%	50	70%

99%	100	94%
99%	150	99%

With greater than 200 subjects per group, all of the HPV-based non-inferiority analyses will have > 99% power. Therefore, there is >92% overall power to show success on all eight HPV endpoints.

Safety Objectives

The subjects receiving MenACWY will provide 95% CI, as demonstrated in the table below, for several possible observed adverse event rates from 0% to 60%. These intervals are provided to indicate the precision afforded with the sample sizes provided within each group and across a combination of groups.

Table 7: 95% Confidence Intervals for MenACWY by Observed Adverse Event Rate

Observed Adverse Event Rate	N = 500 95% Conf. Int.	N = 1000 95% Conf. Int.	N = 1500 95% Conf. Int.
0%	0% to 0.7%	0% to 0.4%	0% to 0.2%
5%	3.2% to 7.3%	3.7% to 6.5%	4.0% to 6.2%
10%	7.5% to 13.0%	8.2% to 12.0%	8.5% to 11.6%
20%	16.6% to 23.8%	17.6% to 22.6%	18.0% to 22.1%
30%	26.0% to 34.2%	27.1% to 32.9%	27.7% to 32.4%
40%	35.7% to 44.4%	36.9% to 43.1%	37.5% to 42.5%
50%	44.5% to 54.5%	46.9% to 53.1%	47.4% to 52.6%
60%	55.6% to 64.3%	56.9% to 63.1%	57.5% to 62.5%

INTERIM ANALYSIS:

No interim analysis of data from this trial is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the BCDM SOP entitled, “Interim Analysis in a Clinical Trial.” After all subjects have completed Visit 3, a preliminary analysis may be performed to assess immunogenicity.

A preliminary analysis may be performed to assess immunogenicity of MenACWY and Tdap and safety (local and systemic reactions and body temperature within 7 days of immunization and SAEs) when all subjects have completed Visit 3.

The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Novartis BCDM standard operating procedure entitled “Interim Analysis in a Clinical Trial.”

TIME AND EVENTS TABLE: Group I

Study Month	**Month 0**		**Month 1**	**Month 2**		**Month 6**		**Month 7**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 181 (-28/+28)	Day 183 (+2) ☎	Day 211 (-4/+7)
Visit Number	**1**		**2**	**3**		**5**		**6**
Obtain Informed Assent and Consent	X							
Medical History	X							
Physical Assessment	X			X		X		
Pregnancy Test[b]	X			X		X		X
Obtain Blood Sample	20 mL		20 mL					20 mL
Administer Study Vaccine(s)	ACWY Tdap HPV			HPV		HPV		
Injection-site Examination	X			X		X		
Distribute/record Diary Card	X		X	X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X			X		X		
Collect/record Concomitant Medications*	X		X	X		X		X
Collect/record Adverse Events*	X		X	X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X
Study Termination								X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group I will not attend Visits 4, 7 and 8.

TIME AND EVENTS TABLE: Group II											
Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	ACWY		Tdap		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group II will not attend Visits 5 and 6.

TIME AND EVENTS TABLE: Group III

Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	Tdap		ACWY		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group III will not attend Visits 5 and 6.

Table 8: Projecting Actual Visits and Visit Windows

Group I

Visit 1	ACWY Tdap HPV	Day 1
Visit 2		(30 days –4/+7 after immunization 1)
Visit 3	HPV	(60 days –4/+7 after immunization 1)
Visit 4		No Visit
Visit 5	HPV	(120 days –28/+28 after immunization 2)
Visit 6		(30 days –4/+7 after immunization 3)
Visit 7		No Visit
Visit 8		No Visit

Group II

Visit 1	ACWY	Day 1
Visit 2	Tdap	(30 days –4/+7 after immunization 1)
Visit 3	HPV	(30 days –4/+7 after immunization 2)
Visit 4	HPV	(60 days –4/+7 after immunization 3)
Visit 5		No Visit
Visit 6		No Visit
Visit 7	HPV	(120 days –28/+28 after immunization 4)
Visit 8		(30 days –4/+7 after immunization 5)

Group III

Visit 1	Tdap	Day 1
Visit 2	ACWY	(30 days –4/+7 after immunization 1)
Visit 3	HPV	(30 days –4/+7 after immunization 2)
Visit 4	HPV	(60 days –4/+7 after immunization 3)
Visit 5		No Visit
Visit 6		No Visit
Visit 7	HPV	(120 days –28/+28 after immunization 4)
Visit 8		(30 days –4/+7 after immunization 5)

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AP	(Statistical) Analysis Plan
BCA	Bactericidal Activity
BCDM	Biostatistics and Clinical Data Management
BCG	Bacille-Calmette-Guerin Vaccine
CFR	Code of Federal Regulations
CI	Confidence Interval
cLIA	Competitive Luminex Immunoassay
CRF	Case Report Form
DCF	Data Clarification Form
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ELISA	Enzyme-linked Immunosorbent Assay
ER Visit	Emergency Room Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HPV	Human papillomavirus
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
ITT	Intention-To-Treat
IVRS	Interactive Voice Response Services
MITT	Modified Intention-To-Treat
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
SAE	Serious Adverse Event
SBA	Serum Bactericidal Assay
SOC	System Organ Class
SOP	Standard Operating Procedure
VLPs	Virus-Like Particles
WFI	Water For Injection
WHO	World Health Organization

Definitions of Terms

End of Trial: The End of Trial corresponds to the last visit of the last subject undergoing the trial (LSLV, Last Subject Last Visit).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial Novartis Vaccines and Diagnostics Srl. is an affiliate of Novartis Vaccines and Diagnostics, Inc.

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

Field Monitor: The person authorized by Novartis Vaccines to monitor clinical trial activities at the trial site.

Local and Systemic Reactions: Selected local and systemic AEs are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of a systemic nature, may under some circumstances, in any individual subject, have a cause that is unrelated to the study vaccine. However, as a matter of convenience and in accordance with common clinical practice, all such events occurring within 7 days after immunization are herein termed “local and systemic reactions.”

Medical Monitor: The Medical Monitor is a physician designated by Novartis Vaccines to be readily available to advise on trial related medical questions or problems and provide the appropriate medical expertise on behalf of the sponsor required for the design and conduct of the trial.

Month, Day: Study months are based upon 30-day cycles. The study day refers to the number of days after enrollment, with the day of first immunization being designated day 1.

Screening: Pre- and/or post-enrollment selection of volunteers to check their eligibility for the trial. A medical examination may be necessary for this purpose.

Serious Adverse Event: Any experience or reaction that suggests a significant hazard, contraindication, side effect, or precaution. These events include any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, is permanently disabling, leads to a congenital abnormality, requires intervention to prevent permanent impairment or damage, or is an important and significant medical event that, based upon appropriate

medical judgment, may jeopardize the subject. Vaccine failure should also be considered as a serious adverse event (SAE).

Study Monitor: The study monitor is the sponsor's designated representative responsible of managing, supervising, and monitoring the overall conduct of the trial.

2.0 ETHICS

2.1 Approval of Study Protocol

Novartis Vaccines or the investigator will provide the Ethics Committee (EC) with all appropriate material, including the informed consent document, according to the local regulation. The EC should also be asked for a written statement regarding the composition of the committee and should comply with GCP and with the applicable regulatory requirement(s). The trial will not be initiated until appropriate EC approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. Prior to enrollment, the sponsor and the investigator must exchange written confirmation that their ethical and legal responsibilities have been observed. The EC and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. Appropriate reports on the progress of the study will be made to the EC and the sponsor by the investigator in accordance with applicable governmental regulations and in agreement with policy established by the sponsor.

2.2 Ethical Conduct and Good Clinical Practice

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), and the applicable regulatory requirement(s) for the country in which the trial is conducted according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs). Specifically, this trial is based on adequately performed laboratory and animal experimentation; the trial will be conducted under a protocol reviewed and approved by an EC; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed. A copy of the ICH GCP guidelines and of the Declaration of Helsinki will be included in the investigator's study file.

2.3 Informed Consent of Subject and Confidentiality

2.3.1 Informed Consent of Subject

The investigator is responsible to obtain informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.

The information about the trial must be given orally and in an understandable form to the legally acceptable representative. Written information about the trial will also be provided. In addition to the explanation of the trial and of the subject's legal rights the information should include that access to original medical records and processing of coded personal

information must be authorized. A person who is qualified according to applicable local regulations must conduct the informed consent discussion. The subject's legally acceptable representative should have the opportunity to inquire about details of the trial and to consider participation.

The informed consent form (ICF) must be signed and dated by the subject's legally acceptable representative and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).

In addition, the subject should be informed about the trial according to his/her capacity to understand the information. Oral and written information is provided. Staff with experience should give the information to minors. If possible, the subject should personally sign and date a written informed consent as affirmative agreement to participate in the clinical trial. Depending on the subject's capability of understanding the given information and forming an opinion the subject's explicit wish to refuse participation must be respected, even if consent is given by the legally acceptable representative. This applies also to the wish to withdraw from the trial.

If the subject or his/her legally acceptable representative is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the informed consent will be orally explained. After the informed consent discussion and after the subject or his/her legally acceptable representative has orally consented to participate in the clinical trial the witness must personally sign and date the consent form to attest that information concerning the clinical trial and the subject's rights were accurately explained to, and apparently understood by the subject or the legally acceptable representative and that informed consent was given freely.

The investigator will provide a copy of the signed informed consent documents to the subject's legally acceptable representative, and will maintain the original(s) in the investigator's study file.

The written informed consent form and any other written information must be revised whenever important new information becomes available that may be relevant to the legally acceptable representative's and subject's consent. Revised written informed consent form, and written information should receive EC's approval before use.

The subject and the subject's legally acceptable representative will be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

2.3.2 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name

appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor. Study findings stored on a computer will be subject to local data protection laws. The subject, or where applicable, the subject's legally acceptable representative(s) will be informed that representatives of the sponsor, EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

The investigator or designee will maintain a personal list of subject numbers and subject identification codes to enable records to be found at a later date.

2.4 Liability and Insurance

The involved parties will be insured, in accordance with applicable laws and regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. The sponsor will provide adequate insurance for the investigator according to regulatory requirement(s). If required by local law, study subjects enrolled into this clinical trial will also be insured against any injury resulting from the clinical study.

3.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to trial initiation, the investigator at the study site must provide Novartis Vaccines a fully executed and signed financial disclosure form. Financial Disclosure Forms must also be completed for all subinvestigators listed on FDA Form 1572 and who will be directly involved in the treatment or evaluation of research subjects in this trial.

The trial will be administered and monitored by employees or representatives of Novartis Vaccines. Study Monitors or Field Monitors will monitor the site on a periodic basis and perform verification of source documentation for each subject. The Medical Monitor will be readily available to provide appropriate medical expertise on trial related medical questions. Novartis Vaccines' Regulatory Affairs or Pharmacovigilance Department will be responsible for the timely reporting of serious adverse events (SAEs).

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TBD

4.0 INTRODUCTION

Neisseria meningitidis causes life-threatening disease worldwide. Based on antigenic differences in their capsular polysaccharide, 13 serogroups of *N. meningitidis* have been identified, with serogroups A, B, C, W135 and Y being responsible for the large majority of invasive meningococcal infections worldwide.

The best option for the control of meningococcal disease is the use of effective vaccines that would include all five of the most common serogroups responsible for invasive disease. Licensed tetravalent polysaccharide vaccines against serogroup A, C, W135 and Y have been available for many years and are widely used. However they do not provide long-term protection and are poorly immunogenic, even in the short-term, in children below 2 years of age.

Based upon the recent, successful development of conjugate vaccines designed to prevent disease caused by *Haemophilus influenzae* type b, Streptococcus *pneumoniae,* and *Neisseria meningitidis* serogroup C, Novartis is developing a conjugate Men ACWY vaccine. This vaccine contains bacterial capsular oligosaccharides for serogroups A, C, W, and Y conjugated to a protein carrier CRM197 (a non-toxic mutant of diphtheria toxin).

A comprehensive and detailed review of investigational Novartis Men ACWY conjugate vaccine is contained in the Investigator's Brochure supplied by the Sponsor while for Boostrix and GARDASIL, please refer to the respective target product profiles. These documents should be reviewed prior to initiating the study.

5.0 STUDY OBJECTIVES

5.1 Immunogenicity Objectives

OBJECTIVES:

Primary Immunogenicity Objectives and Measures

a. To demonstrate that the immune response of MenACWY vaccine when given concomitantly with Tdap and HPV vaccines is not inferior to MenACWY when given alone as directed against *N. meningitidis* serogroups A, C, W and Y following a single dose of vaccine. Response will be measured by serum bactericidal activity using human complement (hSBA) in terms of percentage of subjects with seroresponse, defined as hSBA $\geq$ 1:8 post vaccination if baseline hSBA < 1:4 or achieving a titer post vaccination of at least four times the subject's baseline titer if the subject's baseline titer is $\geq$ 1:4.

b. To demonstrate that the immune response of Tdap given concomitantly with MenACWY is not inferior to the response of Tdap given alone. Immunogenicity response of Tdap is defined as 1) percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL, anti-tetanus toxin ≥1.0 IU/mL and 2) anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), anti-pertactin (anti-PRN) geometric mean concentrations (GMC).

c. To demonstrate that the immune response to MenACWY administered alone one month after Tdap is not inferior to the immune response of MenACWY administered alone one month prior to Tdap as measured by seroresponse directed against *N. meningitidis* serogroups A, C, W, and Y.

Secondary Immunogenicity Objectives and Measures

a. To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is not inferior to the response when HPV is given alone. Immune response against HPV virus-like particles (VLPs) for types 6, 11, 16, and 18 following a third dose of the HPV vaccine will be measured by competitive Luminex immunoassay (cLIA) in terms of:

- The anti-HPV seroconversion (SC), defined as negative for anti-HPV at baseline and anti-HPV greater or equal a HPV type-specific cutoff at one month after the third dose of the vaccine.
- The geometric mean titers (GMTs) to HPV Types 6, 11, 16, 18 at one month after the third dose of the vaccine.

b. To demonstrate that the immune response to Tdap administered alone one month after MenACWY is not inferior to the immune response of Tdap administered alone one month prior to MenACWY with immune response as previously defined for the primary Tdap endpoint.

c. To assess the immunogenicity of MenACWY as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA≥1:4 and hSBA ≥ 1:8, directed against *N. meningitidis* serogroups A, C, W and Y.

d. To assess the immunogenicity of Tdap administered alone or concomitant with MenACWY and HPV as measured by anti-diphtheria and anti-tetanus GMCs and the percentage of subjects with a four-fold rise in antibody over baseline for anti-PT, anti-FHA, and anti-PRN titer.

5.2 Safety Objectives

Safety Objectives and Measures

a. To describe and compare the safety profile following a single dose of MenACWY given alone one month after Tdap to the safety profile following a single dose of MenACWY given alone one month before Tdap vaccine.

b. To describe the safety profile following a single dose of MenACWY given alone or concomitantly with Tdap and HPV vaccine.

c. To describe and compare the safety profile following a HPV given alone to HPV given concomitantly with Tdap and MenACWY vaccine.

6.0 OVERALL STUDY DESIGN

6.1 Overall Study Design and Plan – Description

6.1.1 Overall Study Design

This is a phase 3, open-label, single-center, randomized, controlled study in healthy subjects aged 11-18 years.

Subjects will be included in the study if in good health as judged by physical examination and medical history and if they meet all other inclusion criteria and no exclusion criteria.

Approximately 1620 healthy subjects aged 11-18 years will be randomized in a 1:1:1 ratio to 3 groups. The randomization will be stratified by gender and age group (11-14 years of age, 15-18 years of age). Equal numbers of subjects in each age group are planned to be enrolled (810 subjects into each age stratum).

Table 1

	Month 0	**Month 1**	**Month 2**	**Month 4**	**Month 6**	**Month 7**	**Month 8**	**Month 9**
Group (N)	**Day 1 Visit 1**	**Day 31 Visit 2**	**Day 61 Visit 3**	**Day 121 Visit 4**	**Day 181 Visit 5**	**Day 211 Visit 6**	**Day 241 Visit 7**	**Day 271 Visit 8**
I (540)	Serology Men ACWY+ Tdap + HPV	Serology	HPV		HPV	Serology		
II (540)	Serology Men ACWY	Serology Tdap	Serology HPV	HPV			HPV	Serology
III (540)	Serology Tdap	Serology Men ACWY	Serology HPV	HPV			HPV	Serology
*All subjects will have a telephone call 6 months after final ACWY study immunization, if the subject terminates early from treatment								

A medical history will be obtained and an initial physical exam will be performed to establish eligibility. Blood samples (20 mL) for serological evaluations will be collected in all subjects at Visit 1 (Day 1) prior to administration of study vaccines, at one month after the first immunization (in all study groups), at one month after the second immunization (for group II and III) and at one month after the third HPV immunization (group I-III).

At Visit 1, the investigator, or a qualified person designated by the investigator, should fully inform the subject and his/her parent(s) or guardian(s), when applicable, of all pertinent aspects of the trial and the subject's consent or assent and his/her parent(s)/legal guardian's written informed consent will be obtained after which, subjects will be assigned a screening number. A medical history will be obtained and an initial physical exam will be performed to establish eligibility. A urine pregnancy test will be performed on all females regardless of childbearing potential. Pregnancy tests will be performed at each visit where immunizations are given, prior to each immunization and at the last study visit. If the subjects are in good health, according to the clinical judgment of the investigator, and they meet all inclusion

criteria and no exclusion criteria, they may be enrolled in the study. Enrolled subjects will be identified by a subject number.

After providing a blood sample, subjects will be immunized according to a randomization list. The vaccines will be administered intramuscularly (IM) in the deltoid muscle: Men ACWY vaccine will be administered in the deltoid region of the right arm, Tdap in the deltoid region of the left arm and HPV vaccine in the upper anterolateral region of the thigh. The subjects will remain in the clinic for 30 minutes following immunization to assess for immediate reactions. During Visit 1, subjects and subjects' parents/legal guardians, where applicable, will be instructed on how to measure oral temperature. In addition, subjects and the subjects' parents/legal guardians, where applicable, will be instructed on how to complete a diary card. The diary cards will be collected during the subsequent site visit and a new diary card will be issued. Similar procedures will be followed after each study injection (e.g., after the second and third HPV immunizations).

Subjects, parents or legal guardians will receive a phone call 2 days after each study immunization to query for SAEs and anything of concern to the subject, parent or guardian. If a telephone call is not possible a clinic or home visit may be performed instead. In addition subjects will be queried about significant arm swelling. If significant arm swelling is reported at that time (or any time prior to the next study visit), the subject should be evaluated by study personnel. All events of arm swelling will be recorded on the Adverse Events CRF page, with a comment on the Comments CRF page to detail the event. At this phone call the study staff will answer any questions the subject, parent or guardian may have about diary card completion. The subject, parent or guardian will be reminded of which AEs and concomitant medications to record for the appropriate interval and will remind the subject/parent or guardian of the next scheduled visit.

Medically significant AEs (ER visits and hospitalizations) and all SAEs will be collected for all subjects for the duration of the study. The subjects and/or the subjects' parents/legal guardians, where applicable, will be instructed on how to record medically significant AEs, SAEs, and medications taken as detailed in Table 2.

Subjects will be followed for safety for 30 days after their last vaccination or for 6 months after the last MenACWY immunization, whichever occurs later. This applies also to subjects who terminate early from the study (see Table 2). For subjects who terminate early from the study, before completing a 6 month follow up interval after their last MenACWY injection, a worksheet will be completed for this interval to aid subjects, parents/legal guardians in recollection of events and medications. This worksheet will not be collected and will not be given to subjects who have completed a 6-month safety follow up after MenACWY administration on study.

Table 2

Medical History: Significant past diagnoses including allergies, hospitalizations, major surgeries requiring in-patient hospitalization, any conditions requiring prescription or chronic medication or other significant medical conditions which may impair the assessment of immunogenicity or safety of the study vaccine will be collected	From birth
Immunization History: Immunization history will be collected in subject source. Only diphtheria containing vaccines will be collected in the subject CRF.	From birth
Immediate reactions: Signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 minutes after each immunization
Stayed home due to reaction?	For 7 days after each immunization
Antipyretics/Analgesics used?	For 7 days after each immunization
Temperature: Oral temperature	For 7 days after each immunization
Local reactions: pain, erythema, induration *If persisting beyond Day 7 will be reported as an AE*	For 7 days after each immunization
Systemic reactions: Chills, nausea, malaise, myalgia, arthralgia, headache, and rash *If persisting beyond Day 7 will be reported as an AE*	For 7 days after each immunization
All Adverse Events	For 7 days after each immunization
Adverse Events: AEs that require a medical office visit, consultation and/or results in premature withdrawal from the study.	From Visit 1 through 30 days after last immunization

Medically significant AEs: **AEs requiring Emergency Department visit, or leading to a subject's withdrawal, or hospitalizations** with the exclusion of pre-planned medical office visits or ER visits for routine medical care and common acute conditions such as: • upper respiratory tract infections • otitis media • pharyngitis • urinary tract infections • gastroenteritis • superficial skin infections • contact dermatitis **(Note, the excluded conditions above will NOT be collected or recorded in CRFs.)**	Throughout the study including 6-month follow up period for subjects who terminate early
Serious Adverse Events: A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: • results in death • is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred) • requires or prolongs inpatient hospitalization • results in persistent or significant disability/incapacity • results in a congenital anomaly/birth defect • requires intervention to prevent permanent impairment or damage • is an <u>important and significant medical event</u> that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. *All SAEs will be monitored until resolution and/or the cause is identified.* *If an SAE remains unresolved at study termination, a clinical assessment will be made by the investigator and the Novartis Medical Monitor to determine whether continued follow up of the SAE is warranted.*	Throughout the study
Medications: All prescription and non-prescription medications (with the exception of mineral supplements and vitamins).	For 7 days after each immunization
Prescription medications	From Visit 1 through 30 days after last immunization
Prescription medication taken for medically significant AEs (see medically significant AEs above).	From 30 days after last immunization or through 6-month study follow up phone c12ll for subject

	who terminate early

6.1.2 Planned Duration of Study

Expected subject enrollment interval: Two months.

Duration of individual subject's participation: Up to nine months.

Total duration of study: Approximately eleven months.

End of Trial: Corresponds to the last study visit of the last subject in the trial (LSLV).

6.1.3 Premature Discontinuation of the Study

The sponsor, or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study medication/vaccines etc.) will be returned to the sponsor, or destroyed at the site in accordance with Novartis SOPs.

6.1.3.1 Stopping/Pausing Rules

There are no predetermined stopping rules other than those described in section 6.1.3.

6.2 Discussion of Overall Study Design

Novartis Men ACWY conjugate vaccine has already been tested in several age groups and has been shown to be generally well tolerated and immunogenic. Overall, more than 3200 subjects (from infants up to 55 years old) have received at least one dose of the formulation of Novartis Men ACWY conjugate vaccine (MenACWY) being tested in this study.

A similar tetravalent meningococcal conjugate vaccine, Menactra is licensed and recommended in the United States for active immunization against invasive meningococcal disease in persons 11 to 55 years of age. In adolescents, a combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap) and a vaccine against Human Papillomavirus Recombinant Vaccine [Types 6, 11, 16, 18] (HPV) have also been recommended for routine use recently by ACIP.

Boostrix® is a tetanus, diphtheria, and acellular pertussis (Tdap) booster vaccine available for adolescents 10 through 18 years of age, licensed in the U.S. in 2005. During 2004, a total of 8,897 (34%) of the 25,827 reported pertussis cases in the U.S. occurred among adolescents aged 11–18 years (incidence for adolescents: ~30/100,000 population); 17 states each

reported >100 pertussis cases in adolescents. The incidence of pertussis in adolescents varies widely among states and from year-to-year. During 2000-2004, a total of 11 states had an annual incidence of reported pertussis in adolescents of >50 per 100,000 population during at least 1 year.

GARDASIL® vaccine (Merck & Co., Inc.) was approved by the FDA in June 2006 and is indicated in girls and women 9 to 26 years of age for the prevention of disease caused by Human Papillomavirus (HPV) types 6, 11, 16 and 18. GARDASIL protects recipients against 4 types of HPV, including the two types that cause most cervical cancers and the two types that cause the most genital warts. About 20 million people are infected with HPV in the United States and almost 3,700 women die of cervical cancer in the US each year. The ACIP recommends that GARDASIL be routinely given to girls when they are 11 or 12 years of age, before people become sexually active (i.e., before women are exposed to the viruses). GARDASIL can be started as early as age 9 though, and can also be given to women 13 to 26 years old. GARDASIL is to be given as a three dose series completed over 6 months.

The main objective of the proposed phase 3 study is to describe and compare the safety and immunogenicity profile of a single dose of Novartis Men ACWY administered either concomitantly with the two licensed combined vaccines, Tdap (GlaxoSmithKline, Boostrix®) and Human Papillomavirus Recombinant Vaccine [Types 6, 11, 16, 18], (Merck & Co., Inc., GARDASIL®) or alone to healthy adolescents 11-18 years of age. An important additional objective is to evaluate the safety of serial administration of two diphtheria-containing vaccines (e.g. MenACWY followed by Boostrix). Although both Boostrix and GARDASIL are licensed for younger ages, the lower limit of the age range (11 years) was selected for this study because of earlier decisions for definition of adolescent during the Novartis meningococcal vaccine development program.

This clinical trial on minors has been designed to minimise pain, discomfort, fear and any other foreseeable risks.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Healthy subjects 11-18 years of age will be recruited from the local communities.

Inclusion Criteria

Individuals eligible for enrollment in this study are female and male subjects who have shown to be healthy at screening and who are:

1. 11-18 years of age inclusive who have given their written consent/assent and if applicable, whose parents or legal guardians have given written informed consent at the time of enrollment;

2. virgins (both male and female) with no intention of becoming sexually active during the study period;
3. available for all visits and telephone calls scheduled for the study;
4. in good health as determined by:
   - medical history
   - physical assessment
   - clinical judgment of the investigator
5. who have been properly vaccinated against diphtheria, tetanus, pertussis (i.e., who have received five doses of pediatric DTP/DTaP before the seventh birthday; if the fourth dose was administered on or after the fourth birthday, the fifth dose is not needed);

Informed consent must be obtained for all the subjects before enrollment into the study.

6.3.2 Exclusion Criteria

Exclusion Criteria

Individuals not eligible to be enrolled in the study are those:

1. who are unwilling to give their written assent / consent ;
2. who and/or whose parents or legal guardians are perceived to be unreliable or unavailable for the duration of the study period;
3. who have a positive pregnancy test;
4. who had a previous confirmed or suspected disease caused by *N. meningitidis*;
5. who had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
6. who have previously been immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational). (Exception: Receipt of OMP-containing Hib vaccines is permitted);
7. who have received prior human papillomavirus (HPV) vaccine;
8. who have received investigational agents or vaccines within 90 days prior to enrollment or who expect to receive an investigational agent or vaccine prior to completion of the study;
9. who have received licensed vaccines within one month prior to enrollment or for whom receipt of a licensed vaccine is anticipated during the study period (Exception: Inactivated influenza vaccine may be administered up to 15 days prior to study immunization and no less than 15 days after study immunization);
10. who have received a live viral vaccine within 21 days prior to enrollment;

11. who have experienced, within the 7 days prior to enrollment, significant acute or chronic infection (for example requiring systemic antibiotic treatment or antiviral therapy) or have experienced fever (defined as body temperature ≥ 38°C) within 3 days prior to enrollment;

12. who have any serious acute, chronic or progressive disease such as

    a. history of cancer
    b. complicated diabetes mellitus
    c. advanced arteriosclerotic disease
    d. autoimmune disease
    e. HIV infection or AIDS
    f. blood dyscrasias
    g. congestive heart failure
    h. renal failure
    i. severe malnutrition

(Note: Subjects with mild asthma are eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids are not eligible for enrollment)

13. who have epilepsy, any progressive neurological disease or history of Guillain-Barre syndrome;

14. who have a history of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;

15. who have a condition that is a contraindication to vaccination as indicated in the most recent package inserts (including latex allergy);

16. who have a known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example):

- receipt of immunosuppressive therapy within 30 days prior to enrollment (systemic corticosteroids administered for more than 5 days, or in a daily dose > 1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy)
- receipt of immunostimulants
- receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 90 days prior to enrollment and for the full length of the study

17. who are known to have a bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;

18. who have Down's syndrome or other known cytogenic disorders;

19. who and/or whose families are planning to leave the area of the study site before the end of the study period;

20. who have any condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

6.3.3 Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, a subject may not be eligible for subsequent immunization or may be discontinued from the study following occurrence of:

- febrile convulsions and neurological disturbances after immunization
- hypersensitivity to the investigational vaccine, including latex allergies.
- other suspected side effects that could compromise the subject's well being.

- Significant acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy commenced within the past 7 days;
- Oral temperature of ≥ 38.0°C or presence of an acute systemic illness on the day of immunization;
- Use of systemic corticosteroids (oral, intramuscular or intravenous) administered for more than 5 days or in a daily dose >1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 15 days;
- Use of systemic corticosteroids (oral, intramuscular or intravenous) administered during the study in a daily dose <1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 7 days;
- Any other licensed vaccines can be administered up to 30 days prior to study immunization and no less than 30 days after the study immunization.

Reason for delaying blood draw:

Antibiotics in the blood may interfere with the evaluation of antibodies (i.e., by Serum Bactericidal Activity), therefore a blood draw should be postponed if the subject has received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw.

Withdrawn subjects:

Any subject who, despite the requirement for abstinence, becomes pregnant during the trial will not receive further immunization. The site should maintain contact with the pregnant subject, complete a "Pregnancy Report" CRF as soon as possible, and obtain pregnancy outcome information for "Pregnancy Follow-up" CRF.

Subjects who withdraw early from treatment will be followed up for 6 months after the last immunization. The reason for the early withdrawal will be recorded in detail on the "Study Termination" CRF, and where appropriate, on the "Adverse Events" and/or "Prior and Concomitant Medications" CRF and on the subject's medical records as in section 6.5.4.1.

Whenever possible, the tests and evaluations listed for the termination visit will be carried out.

Withdrawn subjects will not be replaced.

6.4 Vaccines

6.4.1 Vaccines Administered

Approximately 1620 healthy subjects aged 11-18 years will be randomized in a 1:1:1 ratio to 3 groups. The randomization will be stratified by center, gender, and age group (11-14 years of age, 15-18 years of age). Equal numbers of subjects in each age group are planned to be enrolled (810 subjects into each age stratum).

Subjects randomized to Group I will receive MenACWY with Tdap and HPV at month 0 and receive HPV at months 2 and 6 respectively. Subjects randomized to Group II will receive MenACWY at month 0, Tdap at month 1, HPV at month 2, HPV at month 4 and HPV at month 8. Subjects randomized to Group III will receive Tdap at month 0, MenACWY at month 1, HPV at month 2, HPV at month 4 and HPV at month 8.

6.4.2 Identity of Investigational Vaccine

6.4.2.1 Vaccine Composition

Men ACWY conjugate vaccine

The investigational Novartis Men ACWY vaccine is obtained by extemporaneous mixing just before injection of the lyophilized Men A component to be re-suspended with the liquid Men CWY component. The Men ACWY vaccine will be administered IM in the deltoid region of the right arm.

After reconstitution the Men ACWY vaccine will have the following composition per 0.5 mL of injectable solution:

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA (b) (4) µg CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC (b) (4) µg CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW, (b) (4) µg CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY (b) (4) µg CRM_{197}

Sodium chloride	(b) (4)
Sucrose	(b) (4)
Sodium phosphate buffer	(b) (4)
Potassium dihydrogen phosphate	(b) (4)
WFI	(b) (4)

REFERENCE VACCINES, ANTIGEN CONTENT, DOSAGE REGIMEN, ROUTE OF ADMINISTRATION:

HPV vaccine (Merck & Co., Inc. GARDASIL®)

Composition	Quantity per 0.5 mL dose
HPV 6 L1 protein	20 mcg
HPV 11 L1 protein	40 mcg
HPV 16 L1 protein	40 mcg
HPV 18 L1 protein	20 mcg

Other ingredients:

Amorphous aluminum hydroxyphosphate sulphate adjuvant (225 micrograms Al).
Sodium chloride, L-histidine, Polysorbate 80, Sodium borate, Water for Injections.

One 0.5 mL dose of GARDASIL® vaccine will be administered IM in the upper anterolateral area of the thigh.

Tdap vaccine (BOOSTRIX®)

Licensed combined Tdap vaccine Boostrix® (manufactured by GSK Biologicals, Rixensart, Belgium) is supplied as a 0.5 mL dose.

Composition	Quantity per 0.5 mL dose
tetanus toxoid (T)	5 Lf
diphtheria toxoid (d)	2.5 Lf
Inactivated PT	8 µg
filamentous hemagglutinin (FHA)	8 µg
pertactin (PRN)	2.5 µg

Other ingredients:

NaCl (4.5 mg), aluminum adjuvant (not more than 0.39 mg aluminum by assay), ≤ 100 mcg of residual formaldehyde, and ≤ 100 mcg of polysorbate 80 (Tween 80).

One 0.5 mL dose of Boostrix® vaccine will be administered IM in the deltoid area of the left arm.

6.4.2.2 Vaccine Labeling, Storage and Packaging

All vaccine supplies must be stored between 2-8 degrees Celsius. Vaccines that have been stored differently from the sponsor's recommendations must not be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor. Batches of commercially available reference vaccines must be stored separately from normal hospital/practice stocks.

The sponsor will supply the investigational and control vaccines. The investigator (or pharmacist) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.

Itis strongly recommended that a non-frost free laboratory grade refrigerator is used to store the study vaccine. This type of refrigerator is less likely to have wide temperature fluctuations, so it will be more likely to stay within the 2°C to 8°C (35.6°F to 46.4°F) temperature range. A daily refrigerator temperature log must be maintained at the site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder.

Novartis Men ACWY vaccine is identified by a lot number. The last digit of the lot number is a letter that can differ within the same vaccine batch in case multiple packaging and/or labeling processes are performed. This has no impact on the vaccine composition or manufacturing process.

Novartis Men ACWY Conjugate Vaccine will be supplied and packaged as a single dose per box. Each box will contain one vial and one pre-filled syringe. The vial will contain the lyophilized powder of the Men A component and the pre-filled syringe will contain the liquid solution of the Men CWY component.

For each study vaccine, the box label contain the vaccine identifier and the following information:

Protocol Number:
Vaccine description:
Quantity of dosage units, composition:
Store at 2 – 8°C
For Clinical Trial use only
Expiry date:
Lot number:
Sponsor name:

Two tear off labels are on the box. One label should be placed on the administration log. This label contains the Sponsor name, protocol number, a 6-digit blank to be completed with the subject number following randomization, a 3-digit blank to be completed with the subject code, a blank to be completed with the date of vaccine administration and lot number. The other label should be used to place on the barrel of the syringe prior to injection. This label contains the Sponsor name, protocol number and a 6-digit blank to be completed with the subject number.

The Men A vial label will include the identity of the investigational product, a label that includes a 6-digit blank to be completed with the subject number following randomization, the protocol number, the expiry date, the lot number, the required storage conditions, the cautionary statement “For clinical trial use only”, and the directions for use.

The label for the pre-filled syringe containing Men CWY will include the same information as the vial label, except the subject number will not be recorded on the pre-filled syringe.

Tdap vaccine (GSK BOOSTRIX®)

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Boostrix® vaccine will be supplied and packaged as a single 0.5-mL dose per carton. One carton will contain one single dose vial of a fully liquid presentation of Tdap components.

An additional tear-off label including the 6-digit blank to be completed with the subject number following randomization, the protocol number, the sponsors name and location, the cautionary statement “For Clinical trial use only” and the directions for use will be attached to the commercial carton box of the vaccine. The tear-off label will be placed on the

administration log. The commercial vial labels for Boostrix® will remain intact. A syringe label will also be provided and should be placed on the barrel of the syringe prior to injection. This label contains the Sponsor name, protocol number and a 6-digit blank to be completed with the subject number.

HPV vaccine (Merck & Co., Inc. GARDASIL®)

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

GARDASIL is supplied as a carton of one 0.5-mL single dose vial. One carton will contain one single dose vial of a fully liquid presentation of HPV components.

Supplies should be stored in the original nested box with the lid closed to minimize exposure to light. If the refrigerator in which the study vaccine deviates from the 2°C to 8°C (35.6°F to 46.4°F) range, study vaccinations should be suspended and the SPONSOR should be contacted immediately. Vaccine must not be frozen.

An additional tear-off label including the 6-digit blank to be completed with the subject number following randomization, the protocol number, the sponsors name and location, the cautionary statement "For Clinical trial use only" and the directions for use will be attached to the commercial carton box of the vaccine. The tear-off label will be placed on the administration log. The commercial vial labels for GARDASIL® will remain intact. A syringe label will also be provided and should be placed on the barrel of the syringe prior to injection. This label contains the Sponsor name, protocol number and a 6-digit blank to be completed with the subject number.

6.4.2.3 Vaccine Administration

Novartis Men ACWY Conjugate Vaccine

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. Only personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site will administer all vaccines.

The vaccine must be **well shaken** and visually inspected before use. The immunization site should be disinfected with a skin disinfectant (e.g., 70% alcohol). Before immunization, the skin must be dry. **DO NOT inject intravascularly.**

GSK Boostrix® Vaccine

Visually inspect the appropriate vial before use. If any foreign particulate matter and/or variation of physical aspect are observed, DO NOT USE the vaccine and notify Novartis. DO NOT DISCARD the vaccine as it may be returned to Novartis for inspection.

If no particulate matter and/or variation of physical aspect are observed, using a new suitable gauge needle, inject 0.5 mL of product, ensuring no air bubbles are present, in the deltoid area. DO NOT inject intravascularly.

Merck & Co., Inc. GARDASIL® Vaccine

The vaccine should be administered as 3 separate 0.5 ml doses by intramuscular injection. GARDASIL must not be injected intravascularly.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

Prefilled Syringe Use

Inject the entire contents of the syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discolored.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccine, including those with a latex allergy.

Oral temperature ≥ 38°C or serious active infection is reason for delaying immunization. Immunization should also be delayed according to instructions in section 6.3.3.

Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine should be available in case of an anaphylactic reaction. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4.3 Method of Assigning Subjects to Immunization Groups

Approximately 1620 healthy subjects aged 11-18 years will be randomized in a 1:1:1 ratio to 3 treatment groups. The randomization will be stratified by gender and age group (11-14 years of age, 15-18 years of age). Equal numbers of subjects in each age group are planned to be enrolled (810 subjects into each age stratum).

Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 6-digit subject number. The first two digits identify the study site. The next four

digits identify the subject within the site and will be assigned sequentially within each age group and gender stratum. After a subject is enrolled and has received a subject number, the randomization envelope will be opened for that subject. Hidden Entry Envelopes will be used to randomize subjects to the study groups.

6.4.4 Selection of Doses in the Study

The doses used in this study are based upon dose and formulation finding studies conducted in toddlers in Finland, Germany and the United States. In one trial (V59P2, Finland and Germany), more than 500 toddlers received at least one dose of one of 5 formulations of MenACWY (approximately 100 subjects per group). The study results suggested that all of the vaccine formulations were immunogenic; however, the formulation containing 10 µg of antigen of oligosaccharide A and 5 µg each of oligosaccharides C, W, and Y provided a better response to the A component of the vaccine and was therefore selected for further development.

In another trial conducted in the US, 235 toddlers received one dose of three formulations of investigational MenACWY conjugate vaccine; two formulations without adjuvant at a fixed dose of 5 µg or 10 µg per oligosaccharide antigen and one formulation of 5 µg per oligosaccharide adjuvant with aluminum phosphate adjuvant. Although preliminary data suggested improved immunogenicity (as measured by GMTs) for at least one vaccine antigen component (W) in the presence of adjuvant, there was no apparent difference in the responses to the other antigens (A, C and Y). A subsequent toddlers study (V59P7) supported the conclusion that addition of the adjuvant provided no meaningful improvement in immunogenicity. For additional information, please see the Investigator Brochure.

6.4.5 Blinding

The trial is an open-label study; both the study personnel and the subject will know which vaccine is being administered.

6.4.6 Prior and Concomitant Therapy

All prescription medication and non-prescription medication (with the exception of mineral supplements and vitamins) will be recorded for 7 days after each immunization. All prescription medications will be recorded from the day of the first immunization through 30 days after the last immunization. Prescription medications taken to treat medically significant AEs (see Table 2) will also be recorded from 30 days after the last immunization through the follow up phone call 6 months after the last study immunization. A complete vaccine Tdap history from birth will be recorded on entry to the study.

The following concomitant treatments are discouraged and, if used, might lead to a major protocol violation according to the medical judgment of the Novartis Vaccines physician (see exclusion criteria):

- Systemic corticosteroids (oral, intramuscular or intravenous) administered for more than 5 days or in a daily dose >1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 15 days.

- Systemic corticosteroids (oral, intramuscular or intravenous) administered during the study in a daily dose <1 mg/kg/day prednisone or equivalent for ≤ 5 days will delay immunization for 7 days.

- Blood, blood products or a parenteral immunoglobulin preparations;

- Other immunosuppressive agents.

Other licensed vaccines can be administered up to 30 days prior to study immunization and no less than 30 days after the study immunization.

The use of prophylactic antipyretics/analgesics in anticipation of fever or discomfort associated with the injections is strongly discouraged. If antipyretics are given on the day of injection for treatment of fever, the temperature should be retaken and recorded 4 hours after the antipyretic dose to see if further treatment is necessary. This information must be recorded on the subject's diary card and on the appropriate CRF pages.

6.4.7 Immunization Compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the immunizations will be recorded. The investigator will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be returned to the sponsor or destroyed at the investigational site according to the relevant Novartis Vaccines SOP. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.4.8 Adherence to Randomization List

The investigator or the investigator's designate will administer the vaccine indicated in the Hidden Entry Envelope for the individual subject. The Study Monitor will verify adherence to the randomization by checking the immunization records maintained in the investigator's study file.

6.5 Immunogenicity and Safety Variables

6.5.1 Immunogenicity and Safety Measurements Assessed

The Time and Events Table in the Synopsis and section 6.5.5 describe the required evaluations.

6.5.2 Appropriateness of Measurements

The measures of safety used in this study are routine clinical procedures. Selected local and systemic reactions are routinely monitored in vaccine clinical trials as indicators of reactogenicity. They will be closely followed and stringently reported.

6.5.3 Immunogenicity Variables

Diphtheria, tetanus, and pertussis antibody titers will be measured using ELISA. Immune response against HPV VLPs for types 6, 11, 16, and 18 will be measured by cLIA.

The ability of MenACWY to elicit functional bactericidal antibody titers against each serogroup in the presence of human complement (hSBA) will be measured.

Additional analyses to further characterize the immune response to the MenACWY vaccine components may be performed (e.g., SBA using rabbit complement).

6.5.4 Safety Variables

A brief medical history will be obtained and physical examination performed for each subject entered into the study.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.1.1 and 6.5.5.

6.5.4.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and Medical Monitor whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:

Mild: no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational vaccine has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

2. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

3. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

6.5.4.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Of note: a "possible vaccine failure" should be reported as a serious AE only if it resulted in an infectious disease which should have been prevented by the vaccine implied.

Adverse events which do not fall into these categories are defined as **non-serious**.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history CRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

6.5.4.3 Local and Systemic Reactions

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post immunization, will be recorded on the "Local and Systemic Reactions" rather than the "Adverse Events" CRF. If the reaction extends beyond day 7, the reaction will be recorded on the "Adverse Events" CRF.

Local Reactions:

Pain, erythema and induration.

Systemic Reactions:

Chills, nausea, malaise, myalgia, arthralgia, headache and rash.

Other indicators of Reactogenicity:

Stayed home due to reaction, body temperature and use of analgesics/antipyretics.

6.5.4.4 Clinical Laboratory Tests

Not applicable.

6.5.4.5 Documentation/Monitoring/Reporting of Safety Variables

All study subjects will be observed for at least 30 minutes after an immunization for evidence of immediate reactions in general and in particular for symptoms of allergic reactions (such as rashes, itching, or other allergic manifestations). Each subject, or where applicable, the subjects' legally acceptable representative(s) will be instructed to complete a diary card daily for 7 days following each vaccine administration to describe local and systemic reactions, record oral temperature, indicate whether the subject stayed home due to a reaction and/or used analgesics/antipyretics medications, experienced AEs, and took other medications. If a local and systemic reaction continues beyond 7 days after an immunization, it will also be recorded on the "Adverse Events" CRF. If the subject recovers on Day 7, this will be noted on the Local and Systemic CRF. From 8 days after each immunization through the next immunization and through 30 days after the last immunization, subjects will record AEs and medications per Table 2. All solicited adverse events must be reported and documented. The period of observation for adverse events extends from the time the subject receives a study immunization until he/she undergoes the final study examination or phone call, as appropriate. This may include a period before and after an active treatment of an investigational product (study vaccine) or other medication.

Any medical event that occurs after the informed consent form is signed, but prior to the subject receiving study vaccine and is related to a study procedure, will be documented as an adverse event and recorded on the AE CRF. Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the Medical History CRF.

The investigator will monitor all adverse events, regardless of severity, until resolution. All subjects experiencing adverse events whether considered associated with the use of the study vaccine or not must be monitored until symptoms subside, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an "Adverse Events" CRF and on the "Vaccine Serious Adverse Event" form, which is part of the investigator's study file, if the event meets the definition of Serious. All findings in subjects experiencing adverse events must also be reported in the subject's medical records.

In addition, an event resulting in a subject's withdrawal from subsequent immunizations or from follow-up should be reported according to the protocol instructions. All SAEs which

occur during the course of the trial, whether considered to be associated with the study immunization or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor
Olga Mellone, MD
Novartis Biociencias S.A.
Av. Vicente Rao, 90
04706-900 Sao Paulo- SP Brazil
Phone number: +55 11 5532 2465
Mobile phone: + 55 11 8524 5555
Fax number: +55 11 5532 2466
E-mail: olga.mellone@novartis.com

Study Monitor
Caroline Tonussi
Novartis Biociências S.A.
Av. Vicente Rao, 90
04706-900 São Paulo – SP Brazil
Phone number: + 55 11 5532 2461
E-mail: caroline.tonussi@novartis.com

For trial related emergencies out of office hours please contact: **+49 (0) 151 12641663**

As far as possible, all information requested on the "Vaccine Serious Adverse Event" form need to be addressed and the form should be faxed immediately to the Medical Monitor or Study Monitor. The investigator must retain the original. The event must also be documented on the "Adverse Events" CRF. After receipt of the initial SAE report, the Medical Monitor/Study Monitor will review the information and contact the investigator if it is necessary to obtain further information for assessment of the event. Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF(s), in addition to the outcome of the AE. All serious adverse reactions must be reported to the EC, and/or to the applicable regulatory authorities in a timely manner. Adequate documentation will be provided to the sponsor showing that the EC, and/or the applicable regulatory authorities have been properly notified. The sponsor must also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious and non-serious adverse drug reactions to the regulatory authority(ies) and the EC.

If required, a follow up SAE report including all new information obtained on the serious adverse event must be prepared and sent to the Medical Monitor or Study Monitor, or collected by a representative of the sponsor. The report should be marked "Follow-up report."

The investigator will submit, on request, copies of all these reports to the EC and other relevant authorities.

Post-Study Events

All AEs occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine - and therefore a possible adverse drug reaction - must be reported.

6.5.5 Study Procedures and Flowchart

Informed consent must be obtained from the subject, or where applicable, the subject 's legally acceptable representative(s) prior to the performance of any trial specific tests or evaluations, i.e., any unusual or non-routine procedures that involve risk, however trivial, to the subject.

TIME AND EVENTS TABLE: Group I

Study Month	**Month 0**		**Month 1**	**Month 2**		**Month 6**		**Month 7**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 181 (-28/+28)	Day 183 (+2) ☎	Day 211 (-4/+7)
Visit Number	**1**		**2**	**3**		**5**		**6**
Obtain Informed Assent and Consent	X							
Medical History	X							
Physical Assessment	X			X		X		
Pregnancy Test[b]	X			X		X		X
Obtain Blood Sample	20 mL		20 mL					20 mL
Administer Study Vaccine(s)	ACWY Tdap HPV			HPV		HPV		
Injection-site Examination	X			X		X		
Distribute/record Diary Card	X		X	X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X			X		X		
Collect/record Concomitant Medications*	X		X	X		X		X
Collect/record Adverse Events*	X		X	X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X
Study Termination								X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group I will not attend Visits 4, 7 and 8.

TIME AND EVENTS TABLE: Group II											
Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	ACWY		Tdap		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group II will not attend Visits 5 and 6.

TIME AND EVENTS TABLE: Group III											
Study Month	**Month 0**		**Month 1**		**Month 2**		**Month 4**		**Month 8**		**Month 9**
Estimated Study Day and Window[a]	Day 1	Day 3 (+2) ☎	Day 31 (-4/+7)	Day 33 (+2) ☎	Day 61 (-4/+7)	Day 63 (+2) ☎	Day 121 (-4/+7)	Day 123 (+2) ☎	Day 241 (-28/+28)	Day 243 (+2) ☎	Day 271 (-4/+7)
Visit Number	**1**		**2**		**3**		**4**		**7**		**8**
Obtain Informed Assent and Consent	X										
Medical History	X										
Physical Assessment	X		X		X		X		X		
Pregnancy Test[b]	X		X		X		X		X		X
Obtain Blood Sample	20 mL		20 mL		20 mL						20 mL
Administer Study Vaccine(s)	Tdap		ACWY		HPV		HPV		HPV		
Injection-site Examination	X		X		X		X		X		
Distribute/record Diary Card	X		X		X		X		X		X
Assess Local and Systemic Reactions, Oral Temperature; all Adverse Events*	X		X		X		X		X		
Collect/record Concomitant Medications*	X		X		X		X		X		X
Collect/record Adverse Events*	X		X		X		X		X		X
Collect/record SAEs and AEs leading to early study withdrawal*[c]	X	X	X	X	X	X	X	X	X	X	X
Study Termination											X

a. Note: Day of injections/blood draws should be projected from the previous injection, not necessarily completed on the estimated study day listed. Day 1 is defined as the first study immunization.

b. Urine pregnancy test will be performed on all females prior to each immunization and 30 days after their last immunization.

c. Any subject who terminates early will have a follow–up safety phone call 6 months after their last MenACWY injection.

*Refer to Table 2 for further details.

Subjects in Group III will not attend Visits 5 and 6.

Table 8: Projecting Actual Visits and Visit Windows

Group I

Visit 1	ACWY Tdap HPV	Day 1
Visit 2		(30 days –4/+7 after immunization 1)
Visit 3	HPV	(60 days –4/+7 after immunization 1)
Visit 4		No Visit
Visit 5	HPV	(120 days –28/+28 after immunization 2)
Visit 6		(30 days –4/+7 after immunization 3)
Visit 7		No Visit
Visit 8		No Visit

Group II

Visit 1	ACWY	Day 1
Visit 2	Tdap	(30 days –4/+7 after immunization 1)
Visit 3	HPV	(30 days –4/+7 after immunization 2)
Visit 4	HPV	(60 days –4/+7 after immunization 3)
Visit 5		No Visit
Visit 6		No Visit
Visit 7	HPV	(120 days –28/+28 after immunization 4)
Visit 8		(30 days –4/+7 after immunization 5)

Group III

Visit 1	Tdap	Day 1
Visit 2	ACWY	(30 days –4/+7 after immunization 1)
Visit 3	HPV	(30 days –4/+7 after immunization 2)
Visit 4	HPV	(60 days –4/+7 after immunization 3)
Visit 5		No Visit
Visit 6		No Visit
Visit 7	HPV	(120 days –28/+28 after immunization 4)
Visit 8		(30 days –4/+7 after immunization 5)

Visit 1Immunization 1 (Study Day 1- All Groups)

a. Review Inclusion/Exclusion Criteria.

b. Explain and obtain written informed consent/assent from the subject/parent or guardian. Written informed consent must be obtained prior to performance of any study-specific tests or evaluations.

c. Assign the subject a screening number. Complete the screening log.

d. Privately review with females of childbearing potential their ability to become pregnant and commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Obtain medical and immunization history for inclusion and exclusion criteria.

f. Perform pregnancy test on all females.

g. Obtain subject's vital signs, blood pressure, height/weight, and perform an initial physical assessment including oral temperature, a check of general appearance, and systems evaluation for inclusion and exclusion criteria. The physical examination should be performed by the investigator or designee of the investigator – physician, physician assistant, nurse practitioner.

h. Obtain a blood sample via venipuncture from all subjects and store sera from all subjects for serology assays according to the study reference manual.

i. If the subject meets all inclusion and no exclusion criteria and is confirmed for study enrollment, randomize the subject by assigning the subject number in ascending order. Subjects who do not meet all screening criteria at Visit 1 will not be enrolled. Record the subject's screening number on the screening log as well as the subject's informed consent/assent form. A CRF will not be completed for subjects who are not enrolled/randomized. These subjects will be documented only on the screening log. The reason a subject is not enrolled and/or randomized should be recorded on the enrollment/screening log.

j. Administer the subject's assigned injection intramuscularly (see Directions for Administration in Section 6.4.2.3).

k. Give the subject a digital thermometer to be used for the duration of the study and instruct the subject/parent or guardian in its use.

l. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject/ parent or guardian in completion of the diary card.

m. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs, and all concomitant medications. Ensure that the subject/parent or guardian records their 30-minute reactions on the diary card as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through Visit 2.

n. Assess best time to call subject/parent or guardian 2 days after injection and schedule subject to return for Visit 2 (30 days -4/+7 after immunization 1).

o. Process blood samples for testing and store sera from all subjects for serology assays according to the study reference manual.

Telephone Visit (All Groups)

(+2 days after Immunization 1)

a. Call the subject/parent or guardian and query for SAEs, whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 2 Follow-up to immunization 1 (Group I)

(30 days -4/+7 after Immunization 1)

a. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate CRFs.

b. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject/parent or guardian, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

c. Obtain blood sample via venipuncture from all subjects for serology assays according to the Time and Events Table.

d. Dispense interim subject diary card for recording AEs that require medical visits/consultation, SAEs, anything that is otherwise of concern to the subject, AEs that lead to withdrawal from the study and all prescription medication.

e. Schedule subject/parent or guardian to return for Visit 3 (60 days –4/+7 after immunization 1).

f. Process blood samples for testing and store serum for serology assays according to the study reference manual.

Visit 2 Immunization 2 (Groups II & III)

(30 days -4/+7 after immunization 1)

a. Perform a brief physical assessment/evaluate subject for continuing eligibility.

b. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate source documents and CRFs.

c. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

d. Privately review with any females of childbearing potential their commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Perform pregnancy test on all females.

f. Obtain blood sample via venipuncture from all subjects for serology assays according to the Time and Events Table.

g. Administer the subject's assigned injection intramuscularly (see Directions for Administration in Section 6.4.2.3).

h. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject/parent or guardian in completion of the diary card.

i. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs and all concomitant medications. Ensure the subject/parent or guardian records their 30-minute evaluations as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through Visit 3.

j. Assess the best time to call subject/parent or guardian 2 days after injection and schedule Visit 3 (30 days -4/+7 after Immunization 2).

k. Process and store blood samples for serology assays according to the study reference manual.

Telephone Visit (Groups II & III)

(+2 days after Immunization 2)

a. Call the subject/parent or guardian and query for SAEs , whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 3

Immunization 2 (Group I)

(60 days –4/+7 after Immunization 1)

Immunization 3 (Group II and III)

(30 days –4/+7 after Immunization 2)

a. Perform a brief physical assessment/evaluate subject for continuing eligibility.

b. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate source documents and CRFs.

c. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

d. Privately review with any females of childbearing potential their commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Perform pregnancy test on all females.

f. **For Groups II and III only:** Obtain blood sample via venipuncture from all subjects in Groups II and III for serology assays according to the Time and Events Table.

g. Administer the subject's assigned injection intramuscularly (see Directions for Administration in Section 6.4.2.3).

h. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the

subject's source document and appropriate CRF. Take the opportunity to instruct the subject/parent or guardian in completion of the diary card.

i. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs and all concomitant medications. Ensure the subject/parent or guardian records their 30-minute evaluations as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through their next visit.

j. Assess the best time to call subject/parent or guardian 2 days after injection and schedule Visit 4 for Groups II and III (60 days -4/+7 after Immunization at Visit 3) and schedule Visit 5 for Group I (120 days –28/+28 after Immunization at Visit 3).

k. **For Group II and III only:** Process and store blood samples for serology assays according to the study reference manual.

Telephone Visit (All groups)

(+2 days after last Immunization)

a. Call the subject/parent or guardian and query for SAEs, whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 4 – No Visit (Group I)

Visit 4 Immunization 4 (Group II and III)

(60 days –4/+7 after Immunization 3)

a. Perform a brief physical assessment/evaluate subject for continuing eligibility.

b. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate source documents and CRFs.

c. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

d. Privately review with any females of childbearing potential their commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Perform pregnancy test on all females.

f. Administer the subject's assigned injection intramuscularly (see Directions for Administration in Section 6.4.2.3).

g. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject/parent or guardian in completion of the diary card.

h. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs and all concomitant medications. Ensure the subject/parent or guardian records their 30-minute evaluations as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through Visit 7.

i. Assess the best time to call subject/parent or guardian 2 days after injection and schedule Visit 7 (120 days -28/+28 after Immunization at Visit 4).

Telephone Visit (Group II and III)

(+2 days after Immunization 4)

a. Call the subject/parent or guardian and query for SAEs, whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 5: Immunization 3 (Group I)

(120 days – 28/+28 after Immunization 2)

a. Perform a brief physical assessment/evaluate subject for continuing eligibility.

b. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate source documents and CRFs.

c. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

d. Privately review with any females of childbearing potential their commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Perform pregnancy test on all females.

f. Administer the subject's assigned injection intramuscularly (see Directions for Administration in Section 6.4.2.3).

g. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject/parent or guardian in completion of the diary card.

h. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs and all concomitant medications. Ensure the subject/parent or guardian records their 30-minute evaluations as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through Visit 6.

i. Assess the best time to call subject/parent or guardian 2 days after injection and schedule Visit 6 (30 days -4/+7 after Immunization at Visit 5).

Visit 5 – No Visit (Group II and III)

Telephone Visit (Group I)

(+2 days after Immunization 3)

a. Call the subject/parent or guardian and query for SAEs, whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 6: Follow-up to Immunization 3 (Group I)

(30 days – 4/+7 after Immunization 3)

a. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate CRFs.

b. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject/parent or guardian, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

c. Obtain blood sample via venipuncture from all subjects for serology assays according to the Time and Events Table.

d. Perform study exit pregnancy test on all females.

e. Obtain updated contact information from subject, parent/guardian. This includes addresses, telephone numbers, cell phone numbers and email address.

f. Process blood samples for testing and store serum for serology assays according to the study reference manual.

a. Any SAEs ongoing will be followed to resolution or as deemed appropriate by the Investigator or Novartis Medical Monitor.

g. Complete study termination procedures, source and CRF.

Visit 6 – No Visit (Group II and III)

Visit 7 – No Visit (Group I)

Visit 7: Immunization 5 (Group II and III)

(120 days – 28/+28 after Immunization 4)

a. Perform a brief physical assessment/evaluate subject for continuing eligibility.

b. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate source documents and CRFs.

c. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

d. Privately review with any females of childbearing potential their commitment to practice abstinence. Also review with males their commitment to practice abstinence.

e. Perform pregnancy test on all females.

f. Administer the randomized subject's group assigned injection intramuscularly in the deltoid region of the subject's arm (see Directions for Administration in Section 6.4.2.3).

g. At the end of 30 minutes, take the subject's oral temperature and examine the injection site for any local reactions. Evaluate the subject for any systemic reactions and other AEs. Have the subject record these findings on the diary card and record them on the subject's source document and appropriate CRF. Take the opportunity to instruct the subject/parent or guardian in completion of the diary card.

h. Instruct the subject/parent or guardian as appropriate in the evaluation of local and systemic reactions, and recording of oral temperature. Dispense subject's diary card for recording daily oral temperatures, local reactions, systemic reactions, all other AEs and all concomitant medications. Ensure the subject/parent or guardian records their 30-minute evaluations as a guide for subsequent evaluations for days 1 through 7 postinjection. Instruct the subject/parent or guardian to notify the site immediately if they experience any SAEs. Instruct the subject/parent or guardian on which AEs and concomitant medications should be recorded from after 7 days through Visit 8.

i. Assess the best time to call subject/parent or guardian 2 days after injection and schedule Visit 8 (30 days -4/+7 after Immunization at Visit 7).

Telephone Visit (Group II and III)

(+2 days after Immunization 5)

a. Call the subject/parent or guardian and query for SAEs, whole arm swelling and anything of concern to the subject/parent or guardian. Answer any questions the subject/parent or guardian may have about diary card completion. Remind the subject/parent or guardian which AEs and concomitant medications to record for the appropriate interval.

b. Remind the subject/parent or guardian of their next scheduled study visit.

Visit 8 – No Visit (Group I)

Visit 8: Follow-up to Immunization 5 (Group II and III)

(30 days – 4/+7 after Immunization 5)

a. Collect subject diary card and review with the subject/parent or guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. Reconcile diary card with subject source documentation from the phone call 2 days after the last injection. Record information obtained on appropriate CRFs.

b. Obtain history since previous visit of any medical problems, AEs, SAEs, anything that is otherwise of concern to the subject/parent or guardian, and use of concomitant prescription and nonprescription medications. Record information obtained on the appropriate CRFs.

c. Obtain blood sample via venipuncture from all subjects for serology assays according to the Time and Events Table.

d. Perform study exit pregnancy test on all females.

e. Obtain updated contact information from subject, parent/guardian. This includes addresses, telephone numbers, cell phone numbers and email address.

f. Process blood samples for testing and store serum for serology assays according to the study reference manual.

b. Any SAEs ongoing will be followed to resolution or as deemed appropriate by the Investigator or Novartis Medical Monitor.

g. Complete study termination procedures, source and CRF.

Telephone Visit – Early Study Termination (All subjects who terminate early)

(180 days –10/+10 after the subject's last MenACWY immunization)

c. Perform phone call to collect SAEs and all significant medical events (e.g. hospitalizations, pregnancies and ER visits) since the subject last visit. Record all prescription medications taken for treatment or reportable AEs.

d. Follow up on outstanding issues identified at the subject's last visit.

e. Any SAEs ongoing will be followed to resolution or as deemed appropriate by the Investigator or Novartis Medical Monitor.

f. Complete study termination procedures, source and CRF.

All individuals who entered screening, as defined in this section, should be recorded on the "subject screening/enrollment log" where information on the selection of potential participants in the trial should be collected. The reason why an individual was not enrolled or the enrollment date and assigned subject number and code should be recorded by the investigator/study staff. It is the responsibility of the investigator to file this document among those of the investigator's study file to be readily available for an on-site monitoring and/or for inspection by the relevant authorities.

6.5.5.1 Study Evaluations

Blood samples will be obtained according to the Time and Events tables.

6.5.5.1.1 Laboratory Assessments

Not applicable.

6.5.5.1.2 Labeling and Storage of Serum Samples for Serology

At least 10 mL of serum should be available for assays.

All efforts should be made to obtain the required amount of blood from subjects according to the Time and Events Tables. For serology storage, the blood will be centrifuged on the same day as the blood draw. Sera should be pooled from the serum separator tubes and aseptically aliquotted into the tubes provided by Novartis. The serum will be distributed in 4 aliquots, one for original sample and 3 for duplicate samples. Coagulation must be complete before separating the serum from blood components. The aliquots will be stored at a temperature of minus 18°C or below.

Only the cryotubes provided should be used for sera storage. Each serum tube will be labeled with an identifying bar code including subject number, protocol number, barcode identification number and subject code. Serum samples will be sent to the sponsor or will be collected by a representative of the sponsor.

For further information see Appendix B.

Complete instructions for labeling and storage of serum samples are included in the Study Reference Manual.

6.6 Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained at the latest during the initiation visit. During each monitoring visit, qualified staff representing the sponsor will perform source data verification. A CRF collation supplied by the sponsor will be completed for each subject. There will be a separate CRF collation for each randomization group. Trained delegates of the sponsor will check the entries.

Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.

The sponsor's Clinical Quality Assurance (CQA) department will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations. This documentation includes at a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms, the Analysis Plan and the Subject Information and Consent Form model.

6.6.1 Study Monitoring

The clinical study site will be monitored by regular site visits and telephone calls to the investigator by qualified staff representing the sponsor, or their agents following Novartis Vaccines' internal SOP and/or those procedures that are specified by Novartis Vaccines for monitoring trials. The details for monitoring this study (including expected average monitoring frequency and when the first monitoring visit will be performed) will be defined in the monitoring plan. The site monitor will ensure, by frequent communication, that the study is conducted according to the protocol.

CRFs and all original data collected at the site should be available for review during monitoring visits. During these visits, the site monitor should review drug accountability records and document retention including the Investigator's Study File. Additionally, the site monitor should check that clinical study procedures are observed and discuss any problems with the investigator.

6.6.2 Source Data Verification

Inspection and examination of CRFs and source documents (all original recordings, laboratory reports, medical records) - giving due consideration to data protection and medical confidentiality - will be undertaken by representatives of the sponsor. All data not recorded directly on the CRFs as defined in section 6.10 of this study protocol must be verified by checking CRF entries against source documents in order to ensure that the data have been completely and accurately reported as required by the study protocol. Source data verification will be performed and recorded following Novartis Vaccines' internal SOP. The subject or the subject's legally acceptable representative must also allow access to the subject's medical records. Each subject, or the subject's legally acceptable representative, will be informed of this prior to the start of the study.

During or after the clinical study, the regulatory authorities, the EC and/or representatives of the sponsor may request access to all source documents, CRFs and other study documentation for on-site audit or inspection.

6.7 Data Management

All CRF data will be entered in duplicate into a (b) (4) database by BCDM, Novartis Vaccines (except for comments fields on the "Medical History" and "Comments" CRFs which will be entered only once).

Data validation will be performed using the programming languages (b) (4) (b) (4) Data quality assurance will be performed by doing a 100% check of all database updates resulting from the resolution of queries, and by estimating the database error rate with 95% upper confidence limit. The latter must be below the departmental accepted level of 0.5%. Analysis will be performed by BCDM using (b) (4) version (b) (4) according to a predefined Analysis Plan (AP), developed by the study Biostatistician.

All meningococcal serology data analyzed by Clinical Serology, Novartis Vaccines, Marburg will be entered into the (b) (4) database by Clinical Serology, Novartis Vaccines, Marburg. All results will be checked in the laboratory for validity and completeness by three persons before access to the data is granted to BCDM, Novartis Vaccines.

Electronic Data Transfer (EDT) is one method being used by Novartis Vaccines for collecting laboratory data. The full-service laboratory (i.e., central laboratory) will send data as electronic files by a secured method (e.g., via diskette, CD, as an encrypted file attachment

on electronic mail, or as a direct transfer into a specified (b) (4) directory) to the BCDM department, Novartis Vaccines. The data file is pre-processed and loaded by the BCDM Lab Manager into the study database. The laboratory will submit a RESULTS file containing the tests and the results as specified in the protocol. If the laboratory provides the service, it will also submit a Demography (DEMOG) file containing the subject's demographic information. If the file includes results of data blinded to Clinical, the source will provide a separate RESULTS file that will be loaded into a separate laboratory table.

For this protocol, antibody laboratory data will be transmitted via EDT.

6.7.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

6.7.2 Data Protection

Novartis Vaccines respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data [95/46/EC] confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

6.8 Changes in the Conduct of the Study or Planned Analysis

Planned changes in the conduct of the study will be described in protocol amendments; changes in the planned analysis will be described in the clinical study report.

An amendment is a written description of change(s) to or formal clarification of a study protocol.

The EC must be informed of all amendments and if necessary prior review and documented approval/favorable opinion must be sought for ethical aspects. Approval must also be obtained from the authorities, if necessary.

Such amendment will be agreed upon by the sponsor, the investigator, the EC and authorities if necessary prior to implementation.

6.9 Statistical Methods and Determination of Sample Size

6.9.1 Statistical Plans

The statistical evaluation of the results will be performed by BCDM as predefined in the AP. The statistical tables and graphs will be generated using (b) (4) version (b) (4)

Baseline is defined as the time of first immunization.

Definition of populations to be analyzed:

a. Enrolled population: all subjects who have signed an informed consent, undergone screening procedures, and were randomized.

b. Exposed population: all enrolled subjects who actually receive a study vaccination

c. Safety population: all subjects in the exposed population who provide post-baseline safety data

d. Modified Intention-to-treat (MITT) population, Immunogenicity: all subjects in the enrolled population who

   – actually receive all the relevant doses of vaccine
   – provide at least one evaluable serum sample both before and after baseline

e. Per protocol (PP) population, Immunogenicity: all subjects in the MITT population who:

   – receive all the relevant doses of vaccine correctly
   – provide evaluable serum samples at the relevant time points, usually paired
   – HPV analysis only: subjects negative for anti-HPV at baseline (see Appendix C for definition of seropositivity)
   – have no major protocol deviation

   A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

6.9.1.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment will be calculated overall and by vaccine group.

Distributions of subjects by sex and ethnic origin will be summarized overall and by vaccine group. Demographic and baseline data may also be summarized for the MITT and PP populations.

6.9.1.2 Analysis of Immunogenicity Criteria

All immunogenicity analyses will be based on the Per Protocol population.

Primary:

For this study, the analysis of immunogenicity has the following objectives:

- To show that the immunogenicity of MenACWY is not interfered with by concomitant administration of HPV and Tdap vaccines.
- To show that the immunogenicity of Tdap is not interfered with by concomitant administration of MenACWY vaccine.
- To show that administration of Tdap 1 month prior to MenACWY does not interfere with MenACWY response.

As the primary examination of the immune response against N. meningitidis serogroups A, C, W and Y following a single dose of vaccine, immunogenicity will be measured by the percentage of subjects with seroresponse in Group I compared to Group II at visit 2. Seroresponse is defined differently for those subjects with and without baseline titers of at least 1:4. In subjects with a pre-vaccination titer of at least 1:4, seroresponse is defined as a titer at least four times the subject's baseline titer. Subjects with a pre-vaccination titer less than 1:4 will need to attain a post-vaccination titer of 1:8 or greater for seroresponse.

The immunogenicity of MenACWY given concomitantly with HPV and Tdap will be considered non-inferior to the immunogenicity of MenACWY administered alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at 1 month after MenACWY vaccination $\{P_{MenACWY+HPV+Tdap}$ minus $P_{MenACWY}\}$ is greater than -10% for each serogroup (Group I vs. Group II at visit 2). The percentage of subjects with seroresponse and associated two-sided 95% Clopper-Pearson CIs will be computed for each serogroup and for each vaccination group and visit.

A second co-primary examination of the interference of Tdap on the MenACWY response will compare the MenACWY response after serial administration of MenACWY either before or after Tdap and be assessed using rates of seroresponse and non-inferiority criteria as previously described (Group II at visit 2 vs Group III at visit 3).

The immune response one month after primary vaccination to *B. pertussis*, diphtheria and tetanus toxoid will be measured by ELISA. The IgG ELISA concentrations for pertussis will be logarithmically transformed ($base_{10}$). Geometric mean concentrations (GMCs) and associated 95% CI will be computed by exponentiating ($base_{10}$) the corresponding log-transformed means and 95% confidence limits for the log-transformed means. The comparison of the immunogenicity of Tdap given concomitantly with MenACWY to the response of Tdap given alone will be assessed by examining:

- the percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL and anti-tetanus toxin ≥1.0 IU/mL. Tdap concomitant with MenACWY will be considered non-inferior to Tdap alone if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects {$P_{MenACWY+HPV+Tdap}$ minus P_{Tdap}} is greater than -10% for each antigen (Group I vs. Group III at visit 2).

- the ratios of anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA), anti-pertactin (anti-PRN) geometric mean concentrations (GMC). Tdap concomitant with MenACWY will be considered non-inferior to Tdap alone if, for PT, FHA, and pertactin, the lower limit of the two-sided 95% CI for the ratio of the GMCs ($GMC_{MenACWY + Tdap}$ / GMC_{Tdap}) at 1 month after vaccination is > 0.67 (GMC of Group I/GMC of Group III at visit 2).

Secondary: Measures of MenACWY Immunogenicity

As secondary variables, MenACWY hSBA activity will be measured for each serogroup at the relevant timepoints and expressed as GMTs, percent of subjects with hSBA ≥ 1:4, and hSBA ≥ 1:8.

The hSBA GMTs in response to N. meningitidis serogroup A, C, W and Y will be calculated for the following timepoints: Visit 1 (baseline), Visit 2 (Groups I and II only), and Visit 3 (Group III only). GMT increase (geometric mean ratio, [GMR]) at Day 31 (Visit 2) as compared to baseline values (Day 1) will also be calculated. The GMTs, GMRs, two-sided 95% CIs, and median, minimum and maximum values will be calculated for each vaccine group within each serogroup. The GMTs, GMRs and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) titers and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with immunization group, gender, and age group as factors. Titers below the limit of detection will be set to half that limit for the purposes of the analysis.

Secondary: Measures of Concomitant Vaccine Immunogenicity

Immune response against HPV VLPs for types 6, 11, 16, and 18 will be measured by cLIA in terms of the anti-HPV seroconversion (SC) and GMTs. The GMTs, GMRs and two-sided 95% CIs will be constructed by exponentiation (base e) of the least square means of the logarithmically transformed (base e) titers and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with immunization group, gender, and age group as factors.

Immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV given alone if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with anti-HPV seroconversion (SC), at 1 month after the third dose of the HPV vaccine {$P_{HPV + MenACWY}$ minus P_{HPV}} is greater than -5%. Anti-HPV SC is defined for those subjects negative for anti-HPV at baseline, an anti-HPV ≥ HPV type-specific cutoff after vaccination (see Appendix C for HPV-type specific cut-off values). In a separate analysis comparing the immune response of HPV concomitant with MenACWY

to HPV alone, the ratio of GMTs will be assessed to determine non-inferiority. The immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV alone if the lower limit of the two-sided 95% CI of ratio of the GMTs ($GMT_{MenACWY+HPV}$ / GMT_{HPV}) is > 0.50 at 1 month after the third HPV vaccination for each HPV type. Treatment Groups II and III will be combined for the comparison to Group I in the HPV analyses. The success criteria for establishing non-interference of MenACWY on HPV immunogenicity requires that all eight HPV analysis (SC for the 4 HPV types, and GMT ratio for the 4 HPV types) meet the non-inferiority criteria.

The secondary examination of the interference of MenACWY on the Tdap response will compare the Tdap response after serial administration of MenACWY either before or after Tdap and be assessed using the same endpoints are previously described for the primary Tdap criteria (DT: percentage of subjects with response, pertussis antigens: GMC ratio) (Group II at visit 3 vs Group III at visit 2).

6.9.1.3 Analysis of Safety Criteria

Local and Systemic Reactions

The safety profile following a single dose of MenACWY given alone or concomitantly with Tdap and HPV vaccine will be explored (Group I compared to Group II after Visit 1). Similary, the safety profile of HPV given alone will be compared to the profile of HPV given concomitantly with MenACWY and Tdap. Finally, the safety profile of serial administration of MenACWY and Tdap will be assessed.

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

Erythema and induration will be categorized as none (0 mm), 1-25 mm, 26-50 mm, 51-100 mm, and > 100 mm. Oral temperature will be categorized as < 38°C, 38-38.9 °C, 39-39.9°C and ≥ 40°C. All other systemic reactions will be categorized as none, mild, moderate and severe. Each local and systemic reaction will also be categorized as none versus any.

For the local and systemic reaction safety variables, differences among the vaccine groups after each scheduled immunization and after any immunization with respect to all variables (including fever) will be analyzed by using Pearson's chi-square test, or Fisher's Exact test where appropriate.

Other Adverse Events

All the adverse events occurring during the study, judged either as related to immunization or not by the investigator, will be recorded as specified in Section 6.1.1.

The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by immunization group. When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted. Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events will be provided by subject. In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

6.9.1.4 Interim Analysis Planned

No interim analysis of this study is planned. Should it later become necessary, the analysis will be governed by the procedures specified in the Novartis BCDM standard operating procedure entitled “Interim Analysis in a Clinical Trial.”

6.9.1.5 Preliminary Analysis

After all subjects have completed Visit 3, a preliminary analysis may be performed to assess immunogenicity of MenACWY and Tdap and safety (local and systemic reactions and body temperature within 7 days of immunization and SAEs). The results of these analyses will not alter the course of the trial. The analyses will be governed by the procedures specified in the Novartis BCDM standard operating procedure entitled “Interim Analysis in a Clinical Trial.”

6.9.2 Determination of Sample Size

Primary Immunogenicity Objectives:

MenACWY:

Based on the antibody response of adolescents in Novartis study V59P6 who received a single dose MenACWY vaccine, the percentage of subjects with seroresponse at 1 month after vaccination was 80.7%, 75.2%, 84.6%, and 86.1%, respectively, for serogroups A, C, W, and Y. Assuming the subjects in this study will have similar immune response (rates are rounded down to be conservative), the following table shows the power to demonstrate non-inferiority for a given serogroup in the percentage of subjects with seroresponse, based on various group sizes, a noninferiority criterion of –10%, and equal true underlying percentages in each group.

Table 6.9.2-1: Power to Demonstrate Non-Inferiority in the Percentage of Subjects with Seroresponse, Based on Various Group Sizes, and Equal True Underlying Percentages

Serogroup	True Percentage	Power Based on N=450 per group	Power Based on N=500 per group
A	81%	96%	98%
C	75%	93%	95%
W	85%	98%	99%
Y	86%	99%	99%

With 450 subjects per group, the power for the four antigens combined is 87%. If 500 subjects in each group are evaluable, the power for the four combined antigens is increased to 91.8%. Two co-primary objectives are based on this same non-inferiority comparison. Therefore, the combined power for these two endpoints (MenACWY+HPV+Tdap vs. MenACWY alone and MenACWY after Tdap vs. MenACWY alone) is 84.3% for 500 evaluable subjects per group.

Tdap:

Using the ELISA GMC response, immunogenicity of Tdap given concomitantly with MenACWY will be considered non-inferior to Tdap given alone if the lower limit of the two-sided 95% CI of the ratio of the MenACWY+Tdap to Tdap alone GMCs is > 0.67 at 1 month following vaccination. Only the three pertussis antibody responses will be assessed in this manner. From data publicly available regarding the variance of the GMCs for the pertussis antibody response to Boostrix (FDA clinical review 3/15/2005), it was determined that within group standard deviation for the $\log_{10}$ ELISA titers for pertussis toxin, filamentous hemagglutinin, and pertactin were 0.401, 0.351, and 0.622, respectively. These estimates were obtained as the square root of the upper limit of the 80% CI of the within group variance. The following table displays the power for the non-inferiority comparison of the GMC ratio between MenACWY plus Tdap and Tdap administered alone.

Table 6.9.2-2: Power Calculations for Showing Non-Inferiority of Tdap concomitant with MenACWY to Tdap Alone Using a 0.67 Lower Limit of the Two-Sided 95% CI of the Ratio of GMCs of the Pertussis Response (pertussis, FHA, pertactin), Based on Various Group Sizes, and Ratio of Tdap MenACWY:Tdap GMC

Antigen	GMC Ratio	Power N=450 per group	Power N=500 per group
PT (aP)	1.0	99	99
	0.83	94	96
FHA	1.0	99	99
	0.83	98	99
Pertactin	1.0	98	99

	0.83	62	67

Therefore, with 500 subjects per group, the power to demonstrate non-inferiority is 99%, 99%, and 99% for PT, FHA, and pertactin, respectively and an assumed 1.0 ratio. If there are only 450 subjects per group, the power for PT and FHA remains at least 99% and power for the pertactin is 98%.

For the diphtheria and tetanus toxin components of Tdap, immunogenicity response is defined as the percentage of subjects with anti-diphtheria toxin ≥1.0 IU/mL, anti-tetanus toxin ≥1.0 IU/mL. Based on the antibody response quoted in the Boostrix package insert, the percentage of subjects with anti-diphtheria toxin ≥ 1.0 IU/mL and anti-tetanus toxin ≥ 1.0 IU/mL at 1 month after vaccination was 97.3% and 99.3%, respectively. Assuming the subjects in this study will have similar immune response, the following table shows the power to demonstrate non-inferiority for a given toxin in the percentage of subjects with immune response, based on various group sizes, a non-inferiority criterion of –10%, and different true underlying percentages in each group.

Table 6.9.2-3: Power to Demonstrate Non-Inferiority in the Percentage of Subjects with Diphtheria and Tetanus Response, Based on Various Group Sizes, and Various True Underlying Percentages

Antigen	True Percent Tdap	True Percent Tdap+MenACWY	Power Based on N=450 per group	Power Based on N=500 per group
Diphtheria	97%	97%	99%	99%
	97%	92%	91%	94%
Tetanus	99%	99%	99%	99%
	99%	95%	99%	99%

Assuming equal true underlying percentages, a sample size of 450 subjects per group provides 99% power for both anti-diphtheria and anti-tetanus toxin. Therefore, with 450 subjects evaluable for D, T, PT, FHA and pertactin, assuming equal true underlying percentage responders between the two vaccine groups or a GMT ratio of 1.0, the combined power for the Tdap primary endpoints is 94%. If 500 subjects will be evaluable for D, T, PT, FHA and pertactin then power is 95%.

The overall power of this study is based on a multiplication of the power for all three co-primary endpoints. Therefore, combined across the two sets of four MenACWY serogroups and five Tdap antigens, the overall power of the study is 80.1% with 500 evaluable subjects per group. It is estimated that approximately 8% of subjects will be unevaluable for the

immunogenicity analyses. To account for this loss, 540 subjects per group will be randomized.

Secondary Immunogenicity Objectives:

Based on the cLIA GMT response, immunogenicity of GARDASIL given concomitantly with MenACWY will be considered non-inferior to GARDASIL given alone if the lower limit of the two-sided 95% CI of the ratio of the MenACWY+GARDASIL to GARDASIL alone GMTs is ≥ 0.50 at 1 month following the third GARDASIL vaccination. The within group standard deviation for the $\log_e$ cLIA titers is assumed to be 0.721 for HPV type 6, 0.881 for HPV type 11, 1.124 for HPV type 16, and 1.090 for HPV type 18. These estimates were based on the square root of the upper limit of the 80% CI of the within group variance observed for each HPV type in the GARDASIL package insert. The following table displays the sample size necessary to achieve 99% power for the non-inferiority comparison of GMT ratio between MenACWY plus GARDASIL and GARDASIL administered alone.

Table 6.9.2-4: Sample size Calculations Necessary for 99% Power to Show Non-Inferiority of MenACWY concomitant with GARDASIL to GARDASIL Alone Using a 0.50 Lower Limit of the Two-Sided 95% CI of the Ratio of GMTs of the four HPV Types

HPV Type	GMT Ratio	Sample Size For 99% Power
6	1.0 0.83	41 75
11	1.0 0.83	61 111
16	1.0 0.83	98 179
18	1.0 0.83	92 169

As shown, with 100 subjects per group and a ratio of 1.0, the power for each non-inferiority comparison is >99%. Assuming a higher GMT response for the GARDASIL alone group, 200 subjects per group would provide greater than 99% power for each of the comparisons.

In terms of SC, the immunogenicity of HPV given concomitantly with MenACWY will be considered non-inferior to that of HPV given alone if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with anti-HPV seroconversion (SC), at 1 month after the third dose of the HPV vaccine $\{P_{HPV + MenACWY}$ minus $P_{HPV}\}$ is greater than -5%. When HPV vaccination is administered alone, the percentage of subjects with seroconversion at one month after the third dose of the HPV vaccine is very close to 100%. The table below shows, for various sample sizes, the power to reject the null hypothesis for each antigen.

Percent with HPV SC	Sample Size	Power
99%	50	70%
99%	100	94%
99%	150	99%

With greater than 200 subjects per group, all of the HPV-based non-inferiority analysis will have > 99% power. Therefore, there is >92% overall power to show success on all eight HPV endpoints.

Safety Objectives:

The subjects receiving MenACWY will provide 95% CI, as demonstrated in the table below, for several possible observed adverse event rates from 0% to 60%. These intervals are provided to indicate the precision afforded with the sample sizes provided within each group and across a combination of groups.

Table 6.9.2-5: 95% Confidence Intervals for MenACWY by Observed Adverse Event Rate

Observed Adverse Event Rate	N = 500 95% Conf. Int.	N = 1000 95% Conf. Int.	N = 1500 95% Conf. Int.
0%	0% to 0.7%	0% to 0.4%	0% to 0.2%
5%	3.2% to 7.3%	3.7% to 6.5%	4.0% to 6.2%
10%	7.5% to 13.0%	8.2% to 12.0%	8.5% to 11.6%
20%	16.6% to 23.8%	17.6% to 22.6%	18.0% to 22.1%
30%	26.0% to 34.2%	27.1% to 32.9%	27.7% to 32.4%
40%	35.7% to 44.4%	36.9% to 43.1%	37.5% to 42.5%
50%	44.5% to 54.5%	46.9% to 53.1%	47.4% to 52.6%
60%	55.6% to 64.3%	56.9% to 63.1%	57.5% to 62.5%

6.10 Documentation of Study Findings

The sponsor will supply a set of CRF collations. The CRFs do not require carbon paper. The bottom copy must be retained by the investigator, and all other copies will be returned as directed by the sponsor. Instructions on how to complete these forms will be given to the investigator.

The investigator who will sign and date the CRFs must enter all study data. If the investigator authorizes other persons in his/her staff to make entries on the CRF, the names, positions, signatures and initials must be supplied to the sponsor (e.g., a subinvestigator

might join the study after the site initiation visit and be authorized by the investigator to sign the CRFs).

CRFs must be completed during/after each study visit. Arrangements will be made by the monitor to collect completed CRFs periodically. No CRFs are to be mailed to the sponsor without specific authorization.

The investigator must give a reasonable explanation for all missing data.

If corrections are made to entries in the CRF by the investigator or designees, the words or figures must be crossed through, leaving the initial entry legible. The correction must then be dated and initialed. Incorrect entries must not be covered with correcting fluid, obliterated, or made illegible in any way. If further corrections are made after review and signature by the investigator, he/she must confirm and endorse the changes by signing and dating the study termination CRF again.

As part of the conduct of the trial, Novartis Vaccines may have questions about the Case Report Form data after the CRFs are collected from the site. These questions will be documented using Data Clarification Forms (DCFs). Novartis Vaccines will answer the question if the answer is self-evident on "internal" DCFs, but the investigator must review these changes. If the query is not self-evident, Novartis Vaccines will ask the investigator to provide the answer on an "external" DCF and date and sign the DCF. Novartis Vaccines will send the investigator a copy of each completed internal DCF. The investigator will review them and if he/she disagrees with the resolution, he/she will notify the site monitor, who will then generate a new DCF documenting the investigator's correction. The investigator will be requested to file each of the DCFs (either internal or external) for the trial at the study site

Definitions of the DCF types are as follows:

Internal DCF: A DCF for which the resolution is self-evident. It can be answered without changing the meaning of the data or using logical numeric flow (e.g., if an adverse event number is missing, the next number in sequence can be assigned). Internal corrections are defined in either standard or study-specific internal assumptions. The Clinical Data Coordinator or the study monitor can answer an internal DCF. Key safety (e.g., adverse event relationship) or primary endpoint data queries are not to be handled as an internal DCF.

External DCF: A DCF that requires information from the investigator. Key safety (e.g. adverse event relationship) or primary endpoint data queries must be handled as an external DCF.

6.11 Record Retention

Investigators must retain all study records required by Novartis Vaccines and by the applicable regulations in a secure and safe facility. The investigator must consult a Novartis Vaccines representative before disposal of any study records, and must notify the sponsor of

any change in the location, disposition, or custody of the study files. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor or The Committee for Human Medicinal Products (CHMP) requires retention for the maximum period of time permitted by the institution, but not less than 15 years. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

6.12 Use of Information and Publication

It is understood by the investigator that the information generated in this study will be used by the sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigator is obliged to provide the sponsor with complete test results, all study data, and access to all study records.

The sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences.

Any results of medical investigations with the sponsor products and/or publication/lecture/ manuscripts based thereon, shall be exchanged and discussed by the investigator and the sponsor Clinical Research representative(s) 60 days prior to submission for publication or presentation. Due regard shall be given to the sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patient protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

In cases of publications or presentations of material arising from multicenter clinical investigations, the sponsor is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent and the prior review of the sponsor. In case of disagreement amongst the authors, the sponsor will be the final arbiter. The sponsor comments shall be given without undue delay. If they are not accepted, the senior author of the manuscript and the sponsor's representatives shall promptly meet to discuss further and endeavor to agree mutually on the final wording and/or disposition of the publication. The above procedure also applies to information on prematurely discontinued and other not completed studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The sponsor will not quote

from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

All information concerning the study drug supplied by the sponsor in connection with this clinical study, and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, clinical protocol, workbooks if applicable, CRFs, assay methods, the sponsor's technical methodology, and basic scientific data. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to others without prior written consent from the sponsor and shall not be used except in the performance of this clinical study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the sponsor in connection with the development of the study drug. This information may be disclosed as deemed necessary by the sponsor.

The investigator is obliged to provide the sponsor with complete test results and all data derived from this clinical study. Only the sponsor may make information obtained during this clinical study available to the physicians and to the regulatory agencies, except as required by regulation.

Novartis Vaccines and Diagnostics recognize the importance of communicating medical study data and therefore encourage their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be described in the Clinical Study Agreement.

7.0 REFERENCE LIST

1. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81(4):536-8.
2. Campagne G, Chippaux JP, Djibo S, Issa O, Garba A. [Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger)]. Bull Soc Pathol Exot 1999;92(2):118-22.
3. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Carter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894-1901.
4. Ramsay M, Kaczmarski E, Rush M, Mallard R, Farrington P, White J. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev 1997;7(4):R49-54.
5. Decosas J, Koama JB. Chronicle of an outbreak foretold: meningococcal meningitis W135 in Burkina Faso. Lancet Infect Dis 2002;2(12):763-5.
6. Taha M-K, Bichier E, Perrocheau A, Alonso J-M. Circumvention of herd immunity during an outbreak of meningococcal disease could be correlated to escape mutation in the porA gene of Neisseria meningitidis. Infect Immun 2001;69(3):1971-1973.
7. du Chatelet IP, Alonso JM, Taha MK. [Clonal expansion of Neisseria meningitidis W135. Epidemiological implications for the African meningitis belt]. Bull Soc Pathol Exot 2002;95(5):323-4; discussion 324-5.
8. Rosenstein N, Fischer M, Tappero JW. Meningococcal Vaccines. Infectious Disease Clinics of North America 2001;15(1):155-169.
9. Centers for Disease Control and Prevention. Meningococcal disease and college students: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2000;49(RR-7):13-20.
10. Käyhty H, Mäkelä PH, Peltola H. Immunological basis for PRP vaccines. In: Ellis RW, Granoff DM, editors. Development and Clinical Uses of Haemophilus b Conjugate Vaccines. New York, NY: Marcel Dekker Inc.; 1994. p. 1-18.
11. Rosenstein N, Perkins B. Update on Haemophilus influenzae serotype b and meningococcal vaccines. Pediatr Clin North Am 2000;47(2):337-352, vi
12. Cadoz M, Armand J, Arminjon F, Gire R, Lafaix C. Tetravalent (A, C, Y, W 135) meningococcal vaccine in children: immunogenicity and safety. Vaccine 1985;3(3):340-342.
13. King WJ, MacDonald NE, Wells G, Huang J, Allen U, Chan F, et al. Total and functional antibody response to a quadrivalent meningococcal polysaccharide vaccine among children. Journal of Pediatrics 1996;128(2):196-202.

14. Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. Pediatrics 1977;60(5):673-680.

15. Reingold AL, Hightower AW, Bolan GA, Jones EE, Tiendrebeogo H, Broome CV, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet 1985;2(July 20, 1985):114-118.

16. Food and Drug Administration. Product approval informationlicensing action, package insert: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed BOOSTRIX™. Sanofi pasteur. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006.

17. CDC. Final 2004 reports of notifiable diseases. MMWR 2005;54:770.

8.0 INVESTIGATOR AGREEMENT

SIGNATURE PAGE:

A Phase 3, Single-Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis Men ACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents

V59P18

I have read the foregoing protocol and agree to conduct the clinical trial as outlined. I agree to conduct the trial in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____
Investigator Signature Date

Print name:_____

On behalf of Novartis Vaccines I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical trial.

_____ _____
Medical Monitor Signature Date

Print name:_____

APPENDIX A
LIST OF CENTRAL LABORATORIES

The hSBA for MenA, MenC, MenW and MenY will be performed at:
Novartis Vaccines
Klinische Serologie
Gebäude Z26
Emil-von-Behring Str. 76
35041 Marburg
Germany

Tdap ELISA testing will be performed at:
(b) (4)

HPV testing will be performed at (b) (4)

APPENDIX B
SHIPPING AND HANDLING OF LABORATORY SPECIMENS

1. Blood must be centrifuged, and the separated serum frozen as soon as possible after collection. Make sure that coagulation is complete before separating the serum from blood components.
2. Please use the cryotubes provided. Be aware that the maximum-fill volume for these tubes is 90 % of rated capacity, i.e., 3.6 mL, to allow for expansion of the frozen serum. The tubes are marked with a maximum-fill line. Other sizes of cryotubes are not acceptable; if you have an inadequate supply, please contact your Monitor and additional tubes will be provided.
3. Close the tubes before freezing, and check to make sure that the caps are completely tight before packing for shipment.
4. Barcode labels are to be placed lengthwise down the tubes (not wrapped around). Barcodes are machine-readable only when their entire length runs along a flat surface. Please do not write on, make markings through, or otherwise deface the barcode. Make sure that labels are securely attached so that they do not pull away from the tubes after freezing. It is not necessary to fasten the label to the tube with adhesive tape.
5. Before the start of the trial, prepare separate cryoboxes for original and duplicate samples (“Original“ and “Duplicate” labeled cryotubes). After serum has been collected, centrifuged and separated, place labeled tubes in the respective labeled cryoboxes “Original“ and “Duplicate”. Keep the tubes in numerical order by subject number.
6. Freeze tubes at ≤ -18 °C (to -80 °C), in an upright position so that serum does not come into contact with the cap. Tubes may be stored in any convenient position once they are frozen. Do not "quick-freeze" tubes by immersing them in either dry ice or liquid nitrogen; this may crack the tubes.
7. Pack cryotubes for shipment according to the instructions provided. If you have questions, please contact your Monitor.

8. Pack the original shipping log in an envelope inside the cardboard shipping box, on top of the Styrofoam insulated shipper. Fax a copy of the shipping log to:

   Dr. Annette Karsten
   Novartis Vaccines
   Klinische Serologie
   Gebäude Z26
   Emil-von-Behring Str. 76
   35041 Marburg
   Germany
   Tel. +49 (0)6421-39-3439/[3712]
   Fax. +49 (0)6421-39-5826

9. The duplicate samples should be sent still frozen after confirming that the first shipment arrived safely.

APPENDIX C: SEROLOGY PROCEDURES

Retention of Study Records

The raw data, test records, and other laboratory documents generated during the course of the study will be retained in Clinical Serology, Novartis Vaccines, Marburg for 15 years.

Quality Assurance Reviews

Quality Assurance of operations that are routinely performed may be carried out by means of process-based inspections. Technical review on all recorded stages of the assay data will be performed.

Objectives

See Protocol Section 5.1 Immunogenicity Objectives

Sample Storage

Frozen serum samples will be logged and stored at a temperature of minus 18°C ± 6°C in Clinical Serology, Novartis Vaccines, Marburg.

Test Methods and Procedures

Assay name: Diphtheria-ELISA
Antigen: Diphtheria toxoid
Units: IU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: NIBSC standard

Assay name: Tetanus-ELISA
Antigen: Tetanus toxoid
Units: IU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: WHO standard

Assay name: Pertussis-toxin ELISA
Antigen: Pertussis toxin
Units: EU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: FDA Reference sera Lot 3

Assay name: Pertactin-ELISA
Antigen: Pertactin (69K)
Units: EU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: FDA Reference sera Lot 4

Assay name: FHA-ELISA
Antigen: FHA
Units: EU/mL
Internal Standard / Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: FDA Reference Sera lot 3

Assay name: MenA-BCA
Antigen: *Neisseria meningitidis* serogroup A (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none

Assay name: MenC-BCA
Antigen: *Neisseria meningitidis* serogroup C (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none

Assay name: MenW-135-BCA
Antigen: *Neisseria meningitidis* serogroup W-135 (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none

Assay name: MenY-BCA
Antigen: *Neisseria meningitidis* serogroup Y (b) (4)
Units: (b) (4)
Internal Standard/Controls: (b) (4)
Lower Limit of detection: (b) (4)
Standard: none

Assay name: competitive Luminex Immunoassay (cLIA)
Antigen: HPV type 6

Units: milli/Merck units per milliliter (mMU/mL)
Seroconversion/protection limit (b) (4) mMU/mL

Assay name: competitive Luminex Immunoassay (cLIA)
Antigen: HPV type 11
Units: milli/Merck units per milliliter (mMU/mL)
Seroconversion/protection limit: (b) (4) mMU/mL

Assay name: competitive Luminex Immunoassay (cLIA)
Antigen: HPV type 16
Units: milli/Merck units per milliliter (mMU/mL)
Seroconversion/protection limit: (b) (4) mMU/mL

Assay name: competitive Luminex Immunoassay (cLIA)
Antigen: HPV type 18
Units: milli/Merck units per milliliter (mMU/mL)
Seroconversion/protection limit (b) (4) mMU/mL

Equipment

Equipment as listed in the relevant Clinical Serology, SOP and associated documents.

Procedures

All procedures will be carried out according to the relevant SOPs and associated documents from Clinical Serology Marburg, Novartis Vaccines.