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From: Nancy B. Miller, M.D.
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Subject: Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (*S. cerevisiae*) (STN 125126 GARDASIL), manufactured by Merck, Inc.

To: BLA STN# 125126

Through: Joseph Toerner, M.D., M.P.H., Second Clinical Reviewer
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1. Title and General Information

1.1 Title: Medical Officer's Review

1.1.1 STN BLA 125126

1.1.2 Related INDs: ----------

1.1.3 Reviewer's Name: Nancy B. Miller, M.D., DVRPA, HFM-485

1.1.4 Submission Date: 12/7/05

1.1.5 Review Completed: 6/8/06

1.2 Product

1.2.1 Proper Name: Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

1.2.2 Trade Name: GARDASIL

1.2.3 Product Formulation: Each 0.5 mL dose of the vaccine contains:

20 mcg of HPV 6 L1 protein
40 mcg of HPV 11 L1 protein
40 mcg of HPV 16 L1 protein
20 mcg of HPV 18 L1 protein
225 mcg aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant)
9.56 mg of sodium chloride
0.78 mg of L-histidine
50 mcg of polysorbate 80
35 mcg of sodium borate
water for injection

1.3 Applicant: Merck, Inc.

1.4 Pharamcologic Category: Vaccine

1.5 Licensed Indication: Prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine (6, 11, 16, and 18):

- Cervical Cancer
- Genital warts (condyloma acuminata)

And the following precancerous and dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

1.6 Population: Females 9-26 years of age

1.7 Dosage Form and Routes of Administration: The vaccine is administered by intramuscular injection as a three dose series at 0, 2, and 6 months. It will be supplied in cartons of one and ten 0.5 mL single dose vials and one and six pre-filled syringes.

2. TABLE OF CONTENTS

3. **Executive Summary**

The sections of the BLA 125126 in support of clinical efficacy and safety of Gardasil have been reviewed. Additionally, a summary of these data were presented to the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) on May 18, 2006. The conclusions, which follow below, are derived from the review of the data submitted to the BLA and take into account the VRBPAC discussions regarding the proposed use of Gardasil.

The clinical data submitted to the BLA 125126 support the efficacy and safety of Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil) for the following indications:

- Cervical cancer, Cervical Intraepithelial Neoplasia (CIN) Grades 2/3, and Adenocarcinoma in situ (AIS) caused by the types contained within the vaccine (HPV 16, 18, 6, 11).
- Condyloma acuminata caused by types contained within the vaccine (HPV 6, 11, 16, 18).
- Vulvar Intraepithelial Neoplasia (VIN) grades 2/3, and Vaginal Intraepithelial Neoplasia (VaIN) grades 2/3 caused by types contained within the vaccine (HPV 6, 11, 16, 18).
- CIN 1 caused by types contained within the vaccine (HPV 6, 11, 16, 18).

The BLA also included data for consideration of the efficacy of Gardasil to prevent VaIN 1 and VIN 1 associated with HPV types HPV 16, 18, 6 and 11.

Efficacy

Efficacy was assessed in 4 placebo controlled, double blind, randomized Phase II and III clinical studies: Studies 005, 007, 013, and 015[1]. These studies enrolled females 16-23 (Studies 005, 007, and 013) or 16-26 (Study 015) years of age. In each of these studies efficacy was presented for the Per Protocol Efficacy Population (PPE) and several Modified Intent to Treat (MITT) Populations, including the MITT-3 population. The PPE population included subjects who had received all three doses within one year of enrollment, did not have major deviations from the study protocol and were naïve[2] (PCR and serology negative) for assessed vaccine serotypes at baseline and remained PCR negative through Month 7 (one month after dose 3). Efficacy was evaluated beginning one month after administration of the third dose. The MITT-3 population included subjects naïve and non-naïve[3] (PCR and/or serology positive for one or more vaccine serotypes) at baseline, and efficacy was evaluated beginning one month post the first dose of the vaccine. The MITT-3 population may be considered to approximate the general population of women who are HPV naïve and HPV non-naïve, some of whom have HPV related disease at baseline.

[1] Study 005 used the monovalent vaccine type HPV 16. Studies 007, 013, and 015 used Gardasil, except 304 subjects in Protocol 013 who received monovalent HPV 16 as part of a bridging study.
[2] Naïve = seronegative and PCR negative (cervicovaginal [CV] sample) for the relevant HPV type
[3] Non-naïve = seropositive and/or PCR positive (cervicovaginal [CV] sample) for the relevant HPV type

HPV 16/18 related cervical cancer, Cervical Intraepithelial Neoplasia (CIN) grades 2/3, Adenocarcinoma in situ (AIS), or Worse

In November 2001, the Vaccines and Related Biological Products Advisory Committee considered appropriate endoints for licensure of HPV vaccines and determined that given standard of care in developed countries, CIN 2/3 and AIS or worse could be considered a valid surrogate endpoint for cervical cancer. Thus, the primary efficacy endpoint for Study 015 and the combined studies was histopathological diagnosis of CIN 2/3, AIS or worse, with evidence of HPV 16 or 18 in the specimen. Study 015 and the combined studies, analyses showed Gardasil was efficacious in preventing HPV 16- or 18- related CIN 2/3 or AIS in the PPE population (Table 1). When efficacy was evaluated in cases counted one month following the first dose in the MITT-3, which included women who were HPV-naïve and non-naïve to the relevant types, the estimate of efficacy decreased to approximately 39% (MITT-3 population, Table 1).

TABLE 1
Efficacy of Gardasil to Prevent HPV 16- or 18 Related CIN 2/3, AIS, or Worse (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 16, 18 related CIN 2/3, AIS, or Worse	015	PPE	100% (75.8, 100%)
	005, 007, 013, 015	PPE	100% (92.9, 100%)
	015	MITT-3	39.2% (16.9, 55.8%)
	005, 007, 013, 015	MITT-3	39.0% (23.3, 51.7%)

HPV 6-, 11-, 16-, or 18 related Cervical Intraepithelial Neoplasia (CIN) grades 2/3, Adenocarcinoma in situ (AIS), or Worse

When efficacy evaluation was expanded to include CIN 2/3, AIS or worse, with evidence of HPV 6, 11, 16, or 18 in the specimen, i.e., all HPV types included within Gardasil, the point estimate of efficacy was 100% for the PPE population of either Study 015 alone or the combined studies (Table 2). In the efficacy analyses with the MITT-3 population (regardless of baseline vaccine HPV type status) the point estimates of efficacy were 36-41%, lower than demonstrated in the PPE population. Among cases of CIN 2/3 or AIS caused by HPV 6, 11, 16, or 18 in the MITT-3 population, 79% occurred in subjects who had an abnormal Pap test at day 1 and/or who were PCR and/or seropositive for the relevant type at day 1.

TABLE 2
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related CIN 2/3, AIS, or Worse (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related CIN 2/3, AIS, or Worse	015	PPE	100% (81.8, 100%)
	005, 007, 013, 015	PPE	100% (91.0, 100%)
	015	MITT-3	40.9% (19.7, 56.9%)
	005, 007, 013, 015	MITT-3	36.3% (19.4, 49.9%)

HPV 6-, 11-, 16-, or 18 related Condyloma Acuminata
Data to support the prevention of HPV 6, 11, 16, or 18 related condyloma acuminata come from the primary analysis of the PPE population of Study 013 and the analysis of the combined PPE populations in Studies 007, 013, and 015. These analyses demonstrated efficacy of Gardasil to prevent HPV 6, 11, 16, and/or 18 related condyloma acuminata (Table 3). When the population was expanded to include non-naïve subjects (MITT-3 population), vaccine efficacy in Study 013 was 69.5% [95% CI: 48.9, 82.5%] and in the combined analysis 68.5% [95% CI: 57.5, 77.0%].

TABLE 3
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Condyloma Acuminata (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related Condyloma Acuminata	013	PPE	100% (86.4, 100%)
	007, 013, 015	PPE	98.9% (92.3, 100%)
	013	MITT-3	69.5% (48.9, 82.5%)
	007, 013, 015	MITT-3	68.5% (57.5, 77.0%)

HPV 6-, 11-, 16-, or 18 related Vulvar Intraepithelial Neoplasia (VIN) Grades 2/3 or Vaginal Intraepithelial Neoplasia (VaIN) Grades 2/3
A co-primary endpoint for Study 013, included in the composite endpoint "External Genital Lesions," was diagnosis of VIN 2/3 and VaIN 2/3 with evidence of HPV 6, 11, 16, or 18 in the specimen. Data to support this indication also come from an analysis of combined data from Studies 007, 013, and 015. In Study 013 the efficacy of Gardasil against HPV related 6, 11, 16, and/or 18 related VIN 2/3 or VaIN 2/3 was 100% [95%: 30.2, 100%] for the PPE population. In the analysis of combined studies data, analysis of efficacy was 100% [95% CI: 67.2, 100%]. When the 013 or combined studies analyses populations were expanded to include non-naïve subjects (MIIT-3 population) the point estimates of efficacy decreased (Table 4).

Analysis of the ability of Gardasil to prevent 6, 11, 16, and/or 18 related VIN 2/3 was provided for the combined studies. In the PPE population efficacy of Gardasil was 100% [95% CI: 41.4, 100%], and when the population include non-naïve subjects (MITT-3 population), efficacy was 68.1% [95% CI: 22.7, 89.4%] (Table 4).

The ability of Gardasil to prevent HPV 6, 11, 16, and/or 18 related VaIN 2/3 was presented for the combined Studies 007, 013, and 015. Although the point estimates for efficacy were 100% and 78% for the PPE and MITT-3 populations, respectively, the number of VaIN 2/3 cases was small and therefore the lower bound of the 95% CI for both estimates was less than zero. (Table 4).

TABLE 4
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Vulvar Intraepithelial Neoplasia (VIN) Grades 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) Grades 2/3 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 Related VIN Grades 2/3 or VaIN Grades 2/3	013	PPE	100% (30.2, 100%)
	007, 013, 015	PPE	100% (67.2, 100%)
	013	MITT-3	63.7% (<0.0, 91.6%)
	007, 013, 015	MITT-3	73.3% (40.3, 89.4%)
HPV 6, 11, 16, 18 Related VIN Grades 2/3	007, 013, 015	PPE	100% (41.4, 100%)
	007, 013, 015	MITT-3	68.1% (22.7, 88.5%)
HPV 6, 11, 16, 18 Related VaIN Grades 2/3	007, 013, 015	PPE	100% (<0.0, 100%)
	007, 013, 015	MITT-3	77.7% (<0.0, 97.7%)

HPV 6, 11, 16, and/or 18 Related Cervical Intraepithelial Neoplasia (CIN) Grade 1
Efficacy against HPV 6, 11, 16, 18 related CIN 1 is supported by analyses from Study 013 and combined Studies 007, 013, and 015. The Study 013 and combined study analyses showed Gardasil was efficacious in preventing HPV 6, 11, 16, 18 related CIN 1 (Table 5). When the MITT-3 population was assessed, efficacy in Study 013 was 51.0% [95% CI: 21.9, 58.6%], and in the combined studies population efficacy of Gardasil was 54.4% [95% CI: 27.9, 86.1%].

TABLE 5
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Cervical Intraepithelial Neoplasia (CIN) Grade 1 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related CIN 1	013	PPE	100% (84.1, 100%)
	007, 013, 015	PPE	93.1% (81.4, 98.2%)
	013	MITT-3	51.0% (27.0, 67.1%)
	007, 013, 015	MITT-3	54.4% (41.8, 64.5%)

Additional Endpoints Evaluated
HPV 6, 11, 16, and/or 18 Related VIN 1 and VaIN 1
Although the clinical relevance of VIN 1 and VaIN 1 is not well defined, the sponsor provided an assessment of vaccine efficacy against HPV 6, 11, 16, 18 related VIN 1 and HPV 6, 11, 16, 18 related VaIN 1 for Study 013 and combined studies 007, 013, and 015. These data are shown in Table 6. In the PPE population of Study 013, efficacy against HPV 6, 11, 16, 18 related VIN 1 was 100% [95% CI: <0.0, 100%], and in the PPE population of the combined studies 100% [95% CI: 55.4, 100%]. In the MITT-3 population of Study 013, vaccine efficacy against VIN 1 was 16.8% [95% CI: <0.0, 79.9%]. In the combined studies MITT-3 population, efficacy against this endpoint was 57.8% [95% CI: <0.0, 84.0%].

In Study 013, efficacy against HPV 6, 11, 16, 18 related VaIN 1 in the PPE population was 100% [95% CI: <0.0, 100%]. In the combined studies PPE population, efficacy was 100% [95% CI: 30.6, 100%]. In the MITT-3 population of Study 013, efficacy against HPV 6, 11, 16, 18 related VaIN 1 was 88.9% [95% CI: 20.0, 99.7%]. In the combined studies analyses, efficacy in the MITT-3 population was 76.4% [95% CI: 27.7, 94.2%].

TABLE 6
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- and/or 18 Related Vulvar Intraepithelial Neoplasia (VIN) Grade 1 and Vaginal Intraepithelial Neoplasia (VaIN) Grade 1 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related VIN Grade 1	013	PPE	100% (<0.0, 100%)
	007, 013, 015	PPE	100% (41.9, 100%)
	013	MITT-3	16.8% (<0.0, 79.9%)
	007, 013, 015	MITT-3	57.8% (<0.0, 84.0%)
HPV 6, 11, 16, 18 related VaIN Grade 1	013	PPE	100% (<0.0, 100%)
	007, 013, 015	PPE	100% (30.6, 100%)
	013	MITT-3	88.9% (20.0, 99.7%)
	007, 013, 015	MITT-3	76.4% (27.7, 94.2%)

Efficacy Bridge to Females 9-15 years of age

Vaccine efficacy (with histology-confirmed endpoints as described above) was assessed in female subjects 16-26 years of age. Analyses of naïve subjects (PPE population) have higher estimates of efficacy than analyses which also included non-naïve subjects (MITT-3 population). Furthermore, efficacy analyses of non-naïve subjects (seropositive and/or PCR positive at baseline) as compared to naïve subjects for HPV 6, 11, 16, 18 related CIN 2/3, AIS or worse and for HPV 16/18 related CIN 2/3, AIS or worse suggest that Gardasil has limited efficacy in non-naïve subjects. (See discussion in Overall Efficacy Section Efficacy and Tables 275 and 276). Thus, subjects who have not been exposed to HPV serotypes covered by the vaccine, among them younger girls, may benefit from being vaccinated prior to HPV exposure. A serology bridging study, 016, was conducted to compare the immune response of females 10-15 years of age administered Gardasil to that of females 16-23 years of age administered Gardasil. The study demonstrated that following three doses of Gardasil, the GMT and seroresponse rate of females 10-15 years of age was non-inferior to those of females 16-23 years of age.

In addition, the sponsor compared the immune response of females 9-15 years of age (participating in studies 016 and 018) following three doses of Gardasil to the response of females 16-26 years of age who participated in efficacy studies 013 and 015. The sponsor demonstrated that one month following the third dose of Gardasil, the HPV 6, 11, 16, and 18 GMTs of girls 9-15 years of age were non-inferior to those of females 16-26 years of age who participated in the efficacy studies (013 and 015).

Duration of Efficacy
Duration of efficacy has not yet been determined. It is not known whether booster doses will be needed. See post-marketing commitments at the end of the executive summary.

No immune correlate of protection was identified from the Phase III trials. Following three doses of Gardasil at Month 7, the rate of seroconversion was > 99% for all vaccine HPV types in all age groups evaluated. In addition, following three doses of Gardasil, the GMT for each of the vaccine HPV types were higher than those of placebo subjects positive for one or more of the vaccine types at baseline. The duration of immune response has not been determined. However, at 24 months following dose 1, the GMT to each of the vaccine HPV types were at or above the levels seen in unvaccinated subjects with serological evidence of HPV infection to a vaccine type at baseline. The manufacturer has committed to following for long term efficacy and immune response. See post-marketing commitments at the end of the executive summary.

Safety:
In the BLA submission, 11792 subjects had received at least 1 dose of Gardasil in the 5 clinical studies (007, 013, 015, 016, and 018). The majority of these subjects, (10721) were female, and of these, 3422 were females 9-17 years of age who received at least 1 dose of Gardasil. An additional 2146 subjects received at least one dose of the monovalent vaccine in 5 studies (001, 002, 004, 005, and 006).

Table 7
Subjects Administered at least one dose of monovalent HPV vaccine, Gardasil, or placebo in clinical studies in the BLA

Study	Monovalent Vaccine N=2146	Gardasil N=11792	Placebo N=11004
001	112		28(a)
002	82		27(a)
004	428		52(a)
005	1193		1198(a)
006	27		13(b)
007		289	292(c)
013	304	2717	2725(a)
015		6082	6075(a)
016		1525	0
018		1179	594(d)
TOTAL	2146	11792	11004

(a)Placebo = 225 mcg alum as amorphous aluminum hydroxide sulfate AAHS
(b) Placebo = 450 mcg alum as AAHS
(c) Placebo = 146 subjects with 225 mcg AAHS and 146 subjects with 450 mcg AAHS
(d) Placebo = saline placebo
Source: Table 2.7.4:2, p. 62 and Table 2.7.4:3, p. 65, Summary of Clinical Safety, original BLA submission

Injection Site Reactions: In 4 placebo controlled trials in which solicited local and systemic events were monitored using Vaccine Report Cards, a higher proportion of Gardasil recipients experienced local injection site reactions (app. 83%) within the 5 days after any dose, as compared to aluminum adjuvant placebo recipients (77%) or saline

placebo recipients (50%). The majority of injection site adverse events were mild to moderate in severity. The most common local reactions included pain, swelling, and redness.

Systemic Reactions: In studies in which solicited local and systemic adverse events were monitored using Vaccine Report Cards, the proportion of subjects with a systemic adverse event within 15 days after any dose was comparable between the Gardasil recipients (59%) and combined placebo recipients (60%). In study 018, the rates of systemic adverse events were assessed following administration of Gardsil or saline placebo, and the rates of systemic adverse events were lower than observed in other studies but comparable between study groups. Overall, the most common systemic adverse events in both Gardasil and placebo recipients included headache, pyrexia (most low-grade), and nausea.

Discontinuations due to Adverse Events: Few subjects in the Gardasil group (0.18%) and the placebo group (0.15%) discontinued from the trials because of an adverse event. The majority of discontinuations were due to deaths (most after traffic accidents and serious adverse events without apparent association to the vaccine). Please see below and safety summary for details.

Serious Adverse Events: In comparative studies, there were a comparable number of serious adverse events throughout the study in Gardasil recipients (136) or placebo group (125). A comparable **number of subjects** administered Gardasil or placebo reported a Serious Adverse Event (Gardasil N=102, 0.9%; placebo N=99 (1.0%). As of the safety update report of 3/8/06, 59/11778 (0.5%) of Gardasil recipients had experienced an SAE within 15 days after vaccination, and 43 placebo recipients (0.4%) had experienced an SAE within that time frame.

Deaths: In comparative studies, there were 10 deaths among subjects who received Gardasil (0.08%) and 7 (0.07%) among subjects who received placebo. The most common cause of death was motor vehicle accident (4 Gardasil, 3 placebo), followed by suicide/overdose (1 Gardasil, 2 placebo), and pulmonary embolism/DVT (1 Gardasil and 1 placebo). In addition, in the Gardasil group, there were 2 cases of sepsis [1 subject at 395 days following dose 3 and 1 subject at 625 days postdose 3], 1 case of pancreatic cancer (578 days following dose 3), and 1 case of arrhythmia (27 days postdose 1 in a young male with a family history of arrhythmia). In the placebo group, there was 1 case of asphyxia. There was no apparent pattern identified among these events.

Additionally, in Study 005, there was one death in each of the treatment groups: in the HPV 16 vaccine group, there was death in a plane crash 3 years following dose 3 and in the placebo group, there was one suicide 2 years following dose 3.

New Medical Conditions: The number and percentage of new medical conditions reported to occur within the 7 month vaccination period and in the post-seven month vaccination period among subjects who received Gardasil or placebo in comparative studies was reviewed. The incidence rates during the vaccination period in both

treatment groups (49.5% among Gardasil recipients and 49.0% of placebo recipients) were similar. The incidence rates in the post-vaccination period (49.5% among Gardasil recipients and 52.0% among placebo recipients) were also similar.

Pregnancy Outcomes: Overall, pregnancy outcomes among subjects who received Gardasil or placebo in comparative studies were similar: a comparable proportion of pregnancies with live births (Gardasil, 62% and placebo, 60%) and spontaneous abortions (app. 25% in each group) was noted. A similar pattern of adverse events and occurrence in pregnant subjects were noted in the Gardasil group (N=40, 4.2%) and placebo group (N=41, 4.3%). The events in each treatment group were related to conditions leading to C-section, premature labor, and conditions associated with pregnancy, such as pre-eclampsia. For a discussion of congenital anomalies and lactation, see Section 10.3.6.

Additional Indications requested by sponsor
Use in Males: The sponsor had proposed that Gardasil be indicated for use in all adolescents 9-17 years of age, including males. The BLA included safety and immunogenicity data from Studies 016 and 018 in which approximately 1000 males 9-15 years of age were administered a three dose series of Gardasil. No safety or immunogenicity data in males > 15 years was presented in the BLA. A study of efficacy of Gardasil to prevent HPV 6, 11, 16, 18 infection or disease in males 16-23 years of age is underway, and it is anticipated that results will be available in 2008. These results, together with safety data and a serological bridge to younger males (9-15 years of age) will be submitted as a supplement to the Gardasil license to support an indication in males.

Prevention of Vulvar and Vaginal Cancer: It is likely that VIN 2/3 and VaIN 2/3 associated with HPV are precursors to vulvar cancer (especially those which occur in younger women) and most cases of vaginal cancer. The data from the trials demonstrate a favorable impact on the incidence rate of VIN 2/3 and VaIN 2/3 associated with HPV 6, 11, 16, and/or 18. It is expected that with the final closeout of Protocols 013 and 015, there will be additional cases of VIN 2/3 and VaIN 2/3 related to the vaccine types (predominantly HPV 16 and 18). Thus, with additional cases and further consideration of the literature, an indication for the prevention of vulvar and vaginal cancers based on the prevention of VIN 2/3 and VaIN 2/3 may be reconsidered.

Prevention of HPV 6, 11, 16, 18 infection: CBER did not concur with the indication of prevention of HPV 6, 11, 16, and/or 18 infection since almost all preventive infectious disease vaccines are indicated for the prevention of disease caused by the infectious agent.

Issues identified during the clinical review
HPV related disease occurred in Gardasil recipients.
Some non-naïve subjects (sero- and/or PCR positive for one or more vaccine HPV types at baseline) developed HPV disease related to that HPV type(s) or to HPV types not included in Gardasil. Some vaccine recipients who were naïve (i.e., seronegative and PCR negative at baseline) to all four vaccine HPV types developed disease related to an

HPV type not included in the vaccine (although these had not been identified by type specific PCR at the time of the BLA submission). The sponsor has indicated that results of type specific HPV identification for non-vaccine HPV types will be available in spring 2007. In review of the combined datasets (studies 007, 013, and 015), there were an approximately equal number of diagnoses of CIN 3 in naïve Gardasil recipients (40) and naïve placebo recipients (39) in which the HPV type was not confirmed as vaccine related by PCR.

HPV related disease in non-naïve subjects
An exploratory subgroup analyses for study 013 suggested a concern that subjects administered Gardasil who were seropositive and PCR positive for the vaccine relevant HPV types had a greater number of CIN 2/3 or worse cases as compared to such subjects administered placebo. Review of the potential imbalances in baseline characteristics of this subgroup revealed that a higher percentage of these subjects administered Gardasil had High Grade Intraepithelial Lesion (HSIL) on Pap test at baseline [6.5%] as compared to placebo recipients in this subgroup [3.7%]. In addition, a slightly higher proportion of Gardasil recipients in this subgroup [35.9%] had a history of prior cervicovaginal infection as compared to the placebo recipients [32.1%].

A similar exploratory subgroup analysis for Study 015 did not raise a concern for enhancement of cervical disease due to HPV disease. In a combined analysis of Studies 013 and 015, the sponsor presented data to show that of 554 Gardasil subjects who were seropositive and PCR positive at baseline, 5.0% had HSIL at baseline compared to 3.7% of placebo recipients. Despite some difficulties in interpreting subgroup data, the sponsor provided an analysis of the probability of developing a case of HPV 6, 11, 16, 18 related CIN 2 or worse, which was modeled as a function of the following characteristics: smoking status, region, age, lifetime number of sexual partners, number of new sexual partners in the 6 months prior to study start, Pap test diagnosis, using logistic regression. The vaccine group was also included in the model. In the logistic regression modeling for the Combined dataset of Efficacy Studies (Studies 007, 013, and 015), the only variable that was nominally statistically significant was Day 1 Pap test results ($p<0.001$). It is difficult to draw conclusions based on this subgroup analysis. Further surveillance of this subgroup will be included in the post-marketing studies (see below). (Source: Efficacy Information Amendment, Regression Analysis, 6/1/06).

Based on these data, CBER concluded that there was no clear evidence of vaccine related disease enhancement. There is no evidence of therapeutic effect of the vaccine, especially in those PCR positive and seropositive for the relevant HPV type.

Pregnancy Outcomes
Among women who conceived within 30 days of vaccination, there were 5 cases of congenital anomalies in infants born to mothers who received Gardasil and none in infants born to mothers in the placebo group. The five diverse anomalies included the following: hip dysplasia, ankyloglossia with pyloric stenosis, congenital hydronephrosis, congenital megacolon, and club foot. As of 1/25/06, there were 17 congenital anomalies in infants born to Gardasil recipients and 19 to placebo recipients. The pattern of

anomalies does not suggest an association with the vaccine. Pregnancies that occurred in Studies 013 and 015 that had not been completed at the time of the BLA submission will be followed to completion for the close out reports. In addition, a pregnancy registry study is planned as a post-marketing commitment to continue follow-up of pregnancy outcomes. The vaccine is not recommended for use in women known to be pregnant.

Respiratory illnesses and gastroenteritis in the infants whose mothers received Gardasil while breastfeeding

There was a higher proportion of cases of respiratory illnesses and gastroenteritis among infants of mothers who were administered Gardasil during the time they were breastfeeding their infants. Specifically, there were 12 cases of respiratory illnesses in the Gardasil group and 6 in the placebo group (6 within 30 days of vaccination in the Gardasil group and 2 in the placebo group), and 5 cases of gastroenteritis in the Gardasil group as compared to 2 in the placebo group (all cases in the Gardasil group were > 30 days after vaccination). One case in the vaccine group occurred in an infant with anomalous pulmonary venous malformation which is often associated with respiratory distress and chest infections.[4] All cases of respiratory events in both groups who were breastfeeding their infants occurred in the Latin American region. The sponsor noted that most of the subjects who carried a baby to term and breastfed were from this region. Most of these subjects received further doses of the vaccine without an additional respiratory event occurring in these infants. The number of events was small and the times to event post vaccination were variable for these events, and definitive associations could not be made. In infants of mothers who were potentially exposed to study material (and whose mothers were <u>not</u> breastfeeding), there were 13 infants with respiratory events in the placebo group (including 5 infants with neonatal respiratory distress syndrome) compared to 14 infants in the Gardasil group (including 2 infants of neonatal respiratory distress syndrome) in the neonatal period and post-neonatal period. Overall there were 26 respratory events in infants whose mothers received Gardasil, and 19 respiratory events in infants whose mothers received placebo. The package insert will include a cautionary statement about use of Gardasil in women who are breastfeeding their infants. Please see Safety Overview for data presentation and full discussion.

The Vaccines and Related Biological Products Advisory Committeee (VRBPAC) meeting

On May 18, 2006 following presentations by the manufacturer and FDA, the VRBPAC voted unanimously that the data supported the efficacy of Gardasil to prevent HPV 16/18 related cervical cancer, cervical AIS, CIN 2/3 or worse; HPV 6/11/16/18 related VIN 2/3 amd VaIN 2/3; and HPV 6/11/16/18 related condyloma acuminata. After further discussion with the sponsor, HPV 6/11/16/18 related CIN 1 was also added to the indications. The following items and recommendations were also discussed during the meeting:

1. Several members of the Advisory Committee stated that the vaccine would be efficacious in subjects who are naïve for the relevant vaccine HPV type. However, it was acknowledged that type-specific pre-vaccination screening would not be feasible. Therefore, presentation of data showing an apparent lack of efficacy against vaccine HPV types for which a woman is PCR positive and/or

[4] Corbett HJ and Humphrey GM. Pulmonary sequestration. Paediatr Respir Rev. 2004 mar; 5(1): 59-68.

seropositive prior to vaccination was important information. Thus, the package insert should include information from all subjects regardless of baseline HPV status (i.e., the MITT-3 population)

2. Several members of the Advisory Committee emphasized that use of the vaccine does not affect the need for continued Pap test screening as per standard of care. A recommendation was made that a statement regarding this issue should be included in the label.
3. Recommendations were made to assess duration of the immune response and efficacy and assess the need for booster dosing as time progresses.
4. Replacement disease due to HPV types not included in the vaccine should be assessed following licensure.

Post-marketing commitments (See FDA approval letter for final wording of Post-Marketing commitments):

1. Short Term Safety Surveillance: Merck will conduct a short term safety surveillance study of 44,000 vaccinated subjects in a U.S. Managed Care Organization (MCO). Subjects will be followed for 60 days for assessment of general short-term safety (emergency room visits, hospitalizations, and deaths). The subjects will also be followed for 6 months following the third dose for new autoimmune disorders, rheumatologic conditions, or thyroiditis adverse events, and will include ascertainment of new autoimmune disorders, rheumatologic conditions, or thyroiditis. The population will include a sufficient number of children 11-12 years old to permit an analysis of safety outcomes.

2. Pregnancy Registries: Merck will establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL during pregnancy. The U.S. registry will address elements found in CBER's "Guidance for Industry: Establishing Pregnancy Exposure Registries (9/20/2002)."

3. Nordic Long-Term Follow-up Study: Merck is collaborating with four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASIL in approximately 5,500 subjects enrolled in Protocol 015 (one half from the placebo group that will be vaccinated shortly after licensure) for a total of 14 years. This study will assess the long-term effectiveness of the vaccine by detecting HPV 6/11/16/18 related cervical disease including CIN 2/3, AIS, and cervical cancer,VIN 2/3, VaIN 2/3 and vaginal and vulvar cancer due to waning immunity, and assess any replacement with non-vaccine types.

4. Norway Population Study: Provided that GARDASIL is approved in the European Union, the Government of Norway intends to incorporate HPV vaccination into its National Guidelines (Norwegian equivalent of the ACIP). Merck will collaborate with the Norwegian Government to assess the impact of HPV vaccination on: 1) the long-term burden of HPV disease including the incidence of HPV 6/11/16/18-related cervical disease, the incidence of HPV disease caused by types other than HPV 611 1/16/18, the overall incidence of cervical HPV disease, and incidence of HPV-related cancers, pre-cancers (CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and

vaginal cancer) and 2) the interaction between administration of GARDASIL and pregnancy outcomes, especially congenital anomalies, by linking the vaccination registry with the Medical Birth Registry.

5. Final Clinical Study Reports (CSRs) for Protocols 013 and 015: Merck intends to submit completed CSRs when these two Protocols are completed. For Protocols 013 and 015, an end-of-study analysis for "all CIN 2/3, AIS or worse" analysis will evaluate the evidence for replacement of disease due to HPV types 16 and 18 with non-vaccine types (estimated completion spring of 2007). The sponsor will also evaluate all VIN 2/3 and vulvar cancer cases and VaIN 2/3 and vaginal cancer cases in the final analyses.

6. Frequency of Clinical Safety Reporting: Merck agrees to simultaneously provide CBER and the FDA contractor for Vaccine Adverse Events Reporting System (VAERS) all initial post marketing "periodic" adverse experience reports received that are subject to periodic reporting (i.e., not covered under the "15-day Alert report" requirement under 21 CFR 600.80) on a monthly basis. Merck also commits to provide the Quarterly Periodic Adverse Experience Report to the VAERS contractor. This report will contain a recapitulation of all initial reports submitted for the current reporting period and will include all follow up information on VAERS forms collected during that three-month period. Merck commits to providing CBER this information using the aforementioned process, for the first three years after the date of licensure.

7. Duration of Immunity: Merck plans to provide evidence of duration of immunity following administration of GARDASIL, by targeting the following: (i) submission of periodic reports of effectiveness and immunogenicity results from the Nordic Long-Term Follow-up Study to regulators beginning in 4Q 2008, (ii) submission of periodic reports for Protocol 018 (Adolescent Sentinel Cohort), beginning with Month 24 imrnunogenicity and long-term safety data at time of filing in 1Q 2007, (iii) publication of five year immunogenicity data from Protocol 007 in late 2006, and (iv) publication of seven and one half year immunogenicity data from Protocol 005 in 2007.

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls – See reviews by Drs. Gopa Raychudhuri, Robin Levis, Rolf Tafts, Lev Sirota

4.2 Animal Pharmacology/Toxicology – See reviews by Dr. Sally Hargus, Dr. Marion Gruber

CLINICAL REVIEW

5. Clinical and Regulatory Background

5.1 Disease Studied and Available Interventions: Cervical cancer is an important public health problem in the United States, with 9710 new cervical cancer cases and 3700 death due to cervical cancer projected for 2006.[5] Cervical cancer has been associated with Human Papillomavirus (HPV) infection. The applicant, Merck, Inc., began a clinical development program in 1997 with a recombinant HPV virus-like particle (VLP) vaccine for the prevention of cervical cancer. The applicant's clinical development program proceeded using a quadrivalent VLP vaccine, Gardasil, that contains the major capsid protein (L1 protein) from four types of HPV: types 6, 11, 16, and 18. HPV types 16 and 18 are thought to be responsible for more than 50% of cervical cancer, but more than 15 different types of HPV are considered to be "oncogenic" and are associated with the development of cervical cancer. Cervical intraepithelial neopalsia grade 2/3 (CIN 2/3) and adenocarcinoma in situ (AIS) are considered to be precursors to cervical cancer. Condyloma acuminata results from infection with many different types of HPV, but HPV 6 and HPV 11 are thought to be responsible for > 90% of these cases.[6] Therefore, a vaccine that is efficacious in providing protection against HPV types 6, 11, 16, and 18, based on available epidemiological data, might be capable of having an impact in preventing cervical cancer, condyloma acuminata, and other HPV associated diseases related to the vaccine HPV types.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

There are no presently marketed products which are pharmacologically related.

5.3 Previous human experience with the product or related products as well as foreign experience

This information is noted in the summaries of the Phase I studies in this section.

Protocol 001, Protocol 002, Protocol 004, and Protocol 006

Protocol 001: The Safety/Tolerability and Immunogenicity of Research Lot HPV 11 Virus-Like Particle (VLP) Vaccine in College Age Women

Study Period: 9/22/97 – August 7, 2001

Objective: To determine the safety and immunogenicity of four dose formulations of monovalent HPV 11 L1 VLP vaccine (administered at 0, 2 and 6 months) in women 18-25 years of age.

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[5] Jemal A et al. Cancer Statistics, 2006. *CA: A Cancer Journal for Clinicians* 2006;56:106-30.

[6] vanKrogh G et al. *Sex Transm Inf* 2000; 76: 162-8.

Design: Phase I, randomized, double-blind, multicenter, sequential dose-escalating placebo controlled trial (alum control). All subjects, investigators and their staff, and laboratory personnel were blinded to treatment group.

TABLE 8
Protocol 001: Treatment Plan

		Sample Size		
Group	Dosage Level (mcg)	HPV	Placebo	Total
A	10	28	7	35
B	20	28	7	35
C	50	28	7	35
D	100	28	7	35
Total				140

Source: From CSR 001, Table 2, p. 52

Vaccine Products Used:
These were research lot preparations.
10 mcg/0.5 mL HPV 11 L1 VLP vaccine – V501 HSS001 B001
20 mcg/0.5 mL HPV 11 L1 VLP vaccine - V501 HSS001 C001
50 mcg/0.5 mL HPV 11 L1 VLP vaccine - V501 HSS001 D001
100 mcg/ 0.5 mL HPV 11 L1 VLP vaccine - V501 HSS001 E001
Placebo - V501 HSS001 A001 (225 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS)
Each dose of the vaccine contained 225 mcg aluminum as AAHS and ----------.

Population:
The study was conducted at 2 centers in the U.S.
The subjects were healthy females 18-25 years of age, and seronegative for anti-HPV 11. The subjects could not have a history of evidence of HPV related disease. Subjects had to have a negative pregnancy test on the day of vaccination in order to receive study material. (This applies to all other studies reviewed in this document.)

Vaccination schedule: Subjects received vaccine formulation or placebo (0.5 mL) at 0, 2, and 6 months by IM injection in the deltoid muscle.

TABLE 9
Protocol 001: Procedures

Event/Test	Pre-Screening Days -30 to –14)	Randomization Day 0	Mo 1	Mo 2	Mo 3	Mo 6	Mo 7	Mo 9	Mo 12	Mo 13	Mo 18	Mo 24	Mo 36
Gyn history and exam	+								+			+	+
Lab:													
Pregnancy test (a)		+		+		+			+*				
Urine PCR for GC	+								+			+	+
Urine PCR for chlamydia	+								+			+	+
Serum Ab													
RIA	+	+	+	+	+	+	+	+	+	+	+	+	+
Capture -----	+	+	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Neutralization test		+	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Serum for anti-HPV 11 assay development										+			
---------- swabs for HPV PCR	+	+	+		+		+	(+)		+			+
Swab for HSV culture (opt)	+								+			+	+
Ph Vag fluid (opt)	+								+			+	+
Wet mount/trich/BV(opt)	+								+			+	+
Whiff test BV (opt)	+								+			+	+
KOH for yeast (opt)	+								+			+	+
CV ----- for ---------- and HPV PCR	+	+	+		+		+		+			+	+
---------- swab for HPV PCR	+	+	+		+		+		+			+	+
---------- swab for HPV PCR	+	+	+		+		+		+			+	+
Pap test (Thin Prep) cyto	+		+				+		+			+	+
Vaccination (b)		+		+		+			+ *				
Clin f/u for safety		+	+	+	+	+	+			+			

(+) optional test as per Sponsor

a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)

b. Temp and BP prior to each vaccination

c. Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. Phone calls at Day 14 after 1st injection to review all AEs and SAEs. At Months 1, 3, and 7, the study personnel together with the participant will review the VRC. At Months 1, 3, 6, 7, and 13, subjects will be solicited for any gyn health concerns and any SAEs.

*App. ½ of each dose cohort received an additional dose at Month 12. Serum was collected from these subject at M 13.

Source: Table 1, CSR 001, p. 46-7

The **primary immunogenicity endpoint** was the percentage of subjects achieving anti-HPV 11 serum RIA levels $\geq$ 200 mMU/mL at 4 weeks postdose 3 with 95% CIs. **Secondary immunogenicity endpoints** are not all presented here, but include anti-HPV 11 GMTs; evidence of generation of anti-HPV 11 neutralization in Mouse Xenograft Neutralizing test; antibody persistence at 2.5 years postdose 3; assessment of dose response; and anti-HPV 11 levels after a 4th dose of vaccine.

Safety endpoints:
Local reactions within 5 days after vaccination and systemic reactions within 15 days after vaccination, and SAEs throughout study period.

Efficacy Endpoints:
The study was not designed as an efficacy study. However, incident HPV 11 infection, Pap test abnormalities, and histopathological abnormalities are noted below.

Results:
Population

- 140 subjects (28 in each group), 18-26 years of age, were enrolled.
- 116 (82.9%) completed study.
- 24 subjects (17.1%) discontinued from the study. No subject discontinued from the study due to an adverse event. The most common reasons for discontinuation from the study included: lost to follow-up (13 or 9.3%), and refused further participation (9 or 6.4%). 2 (1.4%) subjects discontinued because they became pregnant. 116 subjects entered the booster/persistence phase of the study, and 92 (79.3%) completed this phase. 24 subjects (20.7%) discontinued from this phase of the study, again principally for loss to follow-up (8 or 6.9%) or refusal to participate (16 or 13.8%).
- Mean age: 20.6 years.
- Ethnic distribution: Caucasian (82.1%), Hispanic (9.3%), Black (4.3%), and Asian (3.6%).

Immunogenicity Results
Primary Immunogenicity Analysis
Immunogenicity Populations:
Per protocol: Received 3 vaccinations, were naïve for HPV 6/11 through Month 7, and had serology within specified time course.
All HPV-naïve subjects with serology population: Were also naïve, but could include protocol violators.

The monovalent HPV 11 vaccine induced anti-HPV 11 antibody response at all doses tested. Similar results were seen for this analysis with the HPV 11 naïve with serology population. (Source: CSR, Table 18, pp. 121-122, not shown here)

TABLE 10
Protocol 001: Proportion of Subjects with anti-HPV 11 ≥ 200 mMU/mL and GMTs at Week 4 Postdose 3 (Per Protocol Population)

Treatment Group	N	Percentage of subjects with anit-HPV 11 GMT ≥ 200 mMU/mL by RIA	95% CI for Percentage	GMT (mMU/mL)	95% CI	p-value*
Placebo (N=28)	11	0% (0/11)	0.0, 28.5	<10.0	<10.0, <10.0	1.000
HPV 11 L1 VLP 10 mcg	4	75% (3/4)	19.4, 99.4	594.7	NA	0.313
HPV 11 L1 VLP 20 mcg	15	86.7% (13/15)	59.5, 98.3	517.5	307.8, 870.1	0.004
HPV 11 L1 VLP 50 mcg	13	92.3% (12/13)	64.0, 99.8	538.1	372.6, 777.1	0.002
HPV 11 L1 VLP 100 mcg	17	100% (17/17)	80.5, 100.0	1222.5	867.2, 1723.3	<0.001

Source: CSR 001, Table 17, pp. 119-120 and Table 19, pp. 124

*The lower bound of the 95% CI being > 50% implies that the response rate is statistically significantly greater than the prespecified acceptability criterion (50%) and supports a conclusion of acceptability. A p-value of < 0.025 (1-sided) corresponds to a response rate statistically > 50%.

Neutralization of HPV 11 was also demonstrated at all tested doses.

TABLE 11
Protocol 001: Results of Statistical Analysis Comparing the Percentage of Subjects with HPV 11 Neutralization to 30% at 4 Weeks postdose 3 (Per Protocol population)

Treatment group	n	Observed Percentage of Subjects with HPV 11 Neutralization at Month 7	95% CI for Percentage	p-value
Placebo (N=28)	11	0.0% (0/11)	0.05, 28.5%	1.000
HPV 11 L1 VLP 10 mcg (N=28)	4	100% (4/4)	39.8, 100%	0.008
HPV 11 L1 VLP 20 mcg (N=28)	15	73.3% (11/15)	44.9%, 92.2%	0.001
HPV 11 L1 VLP 50 mcg (N=28)	13	84.6% (11/13)	54.6, 98.1%	<0.001
HPV 11 L1 VLP 100 mcg (N=28)	17	100% (17/17)	80.5, 100%	< 0.001

N=Number of subjects vaccinated
n= Number of subjects contributing to analysis
Source: CSR 001, Table 21, p. 130

Other Secondary Immunogenicity Results

- There was evidence of persistence of anti- HPV 11 antibodies at Month 36.
- Administration of a fourth dose did not appear to produce meaningful increases in the antibody levels at Month 36.

- There was a suggestion of a dose response, in that there was a significant difference between placebo and the 10 mcg dose in percentage of subjects with an anti-HPV 11 antibody level $\geq$ 200 mMU/mL.

Exploratory Efficacy Analyses:
HPV Infection: HPV 11 infection rates could not be assessed, since no HPV 11 infections were detected either in the placebo or in the vaccine groups.
Histopathology Results: Two subjects had visible warts during the study (ANs 0107 and 0260) and underwent genital wart biopsy procedures in the study.

- **AN 0107**: Received HPV 11 L1 VLP 20 mcg vaccine. Genital warts were noted upon examination at the Month 36 study visit. Histologic analysis revealed vulvar intraepithelial neoplasia 1 (VIN 1). PCR analysis showed positivity for **HPV 6** and HPV 18 at Month 36.
- **AN 0260:** Received HPV 11 L1 VLP 50 mcg vaccine, underwent genital wart biopsy on the same day as the Month 36 visit. Histologic analysis revealed mild squamous atypia but results of PCR analysis for biopsy tissue are not available. This subject was PCR negative on swab specimens collected at routine visit intervals for HPV 6, 11, 16, and 18 in all samples up through and including Month 36.

Safety Evaluation:

- Safety data was available for all 140 subjects enrolled in the study.
- In general, there was a higher percentage of subjects reporting an AE after the 1st dose as compared to the 2nd and 3rd doses.
- There was a dose response in the 3 higher doses for injection site reactions.
- Most of the injection site AEs were mild to moderate.
- The overall incidences of systemic AEs were higher in the 50 mcg and 100 mcg doses.
- The most common systemic AEs were headache and URI.

SAEs: One

- **AN 0348:** Depression 75 days postdose 2 of 100 mcg dose.

Deaths: None

Pregnancies: There were 4 pregnancies in the vaccinees. 2/4 delivered healthy infants to term, 1 subject had an elective termination of pregnancy, and 1 subject was lost to follow-up.

Conclusions for Protocol 001: The 20-, 50-, and 100-mcg dose levels of HPV 11 L1 VLP vaccine appear immunogenic. Administration of a fourth dose of HPV 11 L1 VLP vaccine does not produce meaningful increases in antibody levels at Month 36 as compared to the 3 dose regimen. No safety issues were identified from this Phase I trial.

Protocol 002: Safety/Tolerability and Immunogenicity of a Research Lot of HPV 16 Virus-Like Particle (VLP) Vacine in College Age Women
Study Period: 1/5/98 – 10/31/01

Objective: To determine the safety and immunogenicity of three dose formulations of monovalent HPV 16 L1 VLP vaccine in young women 18-25 years of age.

Design: Phase I, randomized, double blind, single center, sequential dose escalating, placebo controlled trial. All subjects, investigators and their staff, and laboratory personnel were blinded to treatment group.

TABLE 12
Protocol 002: Treatment Plan*

Group	Dosage Level (mcg)	Sample Size		
		HPV 16 L1 VLP vaccine	Placebo†	Total
A	10/40	13	4	17
B	40	45	15	60
C	80	24	8	32
Total				109

† The placebo was identical for all groups.
HPV = Human papillomavirus; VLP = Virus-like particle.

*Originally, subjects were to be randomized 3:1 to panels of sequentially higher doses of HPV 16 L1 VLP vaccine or placebo. However, early in the study, the 10 mcg dose showed decreased immunogenicity in mice. Therefore, subjects randomized to the 10 mcg dose were subsequently given the 40 mcg dose.
Source: Table 3, CSR, p. 48

Vaccine Products Used:
These were research lot preparations.
10 mcg/0.5 mL HPV 16 L1 VLP vaccine - V501 HSS002D001
40 mcg/0.5 mL HPV 16 L1 VLP vaccine V501 HSS002C001
80 mcg/0.5 mL HPV 16 L1 VLP vaccine V501 HSS002B001
Placebo - V501 HSS002A002 (225 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS in saline)
Each dose of vaccine contained 225 mcg aluminum as AAHS and ----------.

Population: The study was conducted at one center in the U.S.
In general, the subjects were healthy 18-25 year old women who were naïve for HPV 16 infection at baseline (women enrolled were to be HPV 16 seronegative and PCR negative at screening), had 0-5 lifetime sexual partners, and had no history of abnormal Pap.

Vaccination Schedule: Subjects received vaccine formulations or placebo (0.5 mL) at 0, 2, and 6 months by IM injection in the deltoid.

Primary immunogenicity endpoint: The % of subjects achieving anti-HPV 16 serum RIA levels ≥20 mMU/mL 1 month following the third injection of vaccine/placebo.

Secondary and exploratory immunogenicity endpoints were also evaluated, e.g., anti-HPV 16 serum RIA GMTs.

Safety Endpoints:
Primary safety endpoints were incidences of SAEs that were vaccine related and severe injection site AEs.
Also assessed, but not considered primary safety endpoints, were local reactions and fevers within 5 days of vaccination and systemic reactions within 14 days of vaccination.

Efficacy Endpoints:
Efficacy was not an endpoint, but exploratory endpoints included the rate of incident HPV 16 infection, the rate of incident HPV 6, 11, and 18 infections, the incidence of HPV related disease, and the association between PCR responses and Pap test results.

Surveillance for Protocol 002:

TABLE 13

Protocol 002: Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Pre-Screening Days -30 to –14)	Randomization Day 0	Mo 2	Mo 3	Mo 6	Mo 7	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36
Gyn history and exam	+						+		+		+
Lab:											
Pregnancy test (a)		+	+		+						
Urine PCR for GC	+						+		+		+
Urine PCR for chlamydia	+						+		+		+
Urine for HPV PCR		(+)		(+)		(+)	(+)		(+)		(+)
Serum for hep B, HIV, syphilis (if indicated)	+	+	+	+	+	+	+		+		+
Serum Ab											
RIA	+	+	+	+	+	+	+	+	+	+	+
----------	+	+	(+)	(+)	(+)	(+)	+	(+)	(+)	(+)	(+)
Blood for -------- assay		+		+		+	+		+		
---- swab for HPV PCR	+				+		+		+		
---------- swabs for HPV PCR	+	+		+		+	+		+		+
Swab for HSV culture (opt)	+						+		+		+
Ph Vag fluid (opt)	+						+		+		+
Wet mount/trich/BV(opt)	+						+		+		+
Whiff test BV (opt)	+						+		+		+
KOH for yeast (opt)	+						+		+		+
CV ------ for ----- and HPV PCR	+	+		+		+	+		+		+
---------- swab for HPV PCR	+	+		+		+	+		+		+
---------- swab for HPV PCR	+	+		+		+	+		+		+
Pap test (Thin Prep) cyto	+			+		+	+		+		+
Vaccination (b)		+	+		+						
Clin f/u for safety		+	+	+	+	+					

(+) optional test as per Sponsor

a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)

b. Temp, wt. and BP prior to each vaccination

c. Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. Phone calls at Day 14 after 1st injection to review all AEs and SAEs. At Months 3, and 7, the study personnel together with the participant will review the VRC. At Months 2, 3, 6, and 7, subjects will be solicited for any gyn health concerns and any SAEs.

Source: Table 2, CSR 002, p. 42-3

Primary Safety Objective: addressed AEs (similar to Protocol 001).

Populations Analyzed
Per Protocol Population: naïve for HPV 16 through Month 7, received all 3 doses of vaccine, and serology within day ranges and after 3rd dose.
All HPV 16 naïve subjects with serology data: Naïve for HPV 16 through Month 7 had month 7 serology results, and includes violators.

Results
Population (all study groups)
- 109 subjects, 18-25 years of age, entered the study and received at least one dose of vaccine.
- 103 subjects completed the vaccination phase (up to Month 7).
- Mean age: 20.3 years.
- Ethnic Distribution: 78% Caucasian, 15.6% Asian, 1.8% black, 1.8% Caucasian/Asian, and 0.9% Hispanic.
- Percentage of subjects with a history of abnormal Pap or genital warts: 1.8% for each of these diagnoses.

Immunogenicity Data:
Primary Immunogenicity Analysis: The 40-mcg and 80-mcg dose levels met the acceptability criterion for the primary hypothesis.
These results were consistent for both the per-protocol and all HPV 16-naïve subjects with serology data populations. (Source for latter: Table 55, CSR 002, p. 216-7, not shown here)

TABLE 14
Protocol 002: Immunogenicity Summary of Percentage of Subjects Achieving Anti-HPV 16 RIA ≥ 20 mMU/mL and GMTs with 95% CIs (Per Protocol Population)

Treatment Group	Time Point	n	**Percentage of Subjects with Serum HPV 16 RIA Levels ≥ 20 mMU/mL**	95% CI	**GMT mMU/mL**	95% CI
Placebo (N=27)	Month 7	23	**0% (0/23)**	0.0, 14.8%	**< 6.0**	<6.0, <6.0
HPV 16 L1 VLP 10/40 mcg (N=13)	Month 7	8	**100% (8/8)**	63.1, 100%	**447.9**	185.3, 1082.9
HPV 16 L1 VLP 40 mcg (N=45)	Month 7	35	**100% (35/35)**	90.0, 100%	**823.6**	630.9, 1075.2
HPV 16 L1 VLP 80 mcg (N=24)	Month 7	20	**100% (20/20)**	83.2, 100%	**732.3**	420.7, 1274.6

N=Number vaccinated
n=number contributing to the summary
Source: Table 22, CSR 002, p. 112

TABLE 15
Protocol 002: Results of Statistical Analysis of Acceptability of Immune Response (Percentage of Subjects with HPV 16 Serum RIA Levels ≥ 20 mMU/mL at Month 7 (4 weeks postdose 3) (Per Protocol Population)

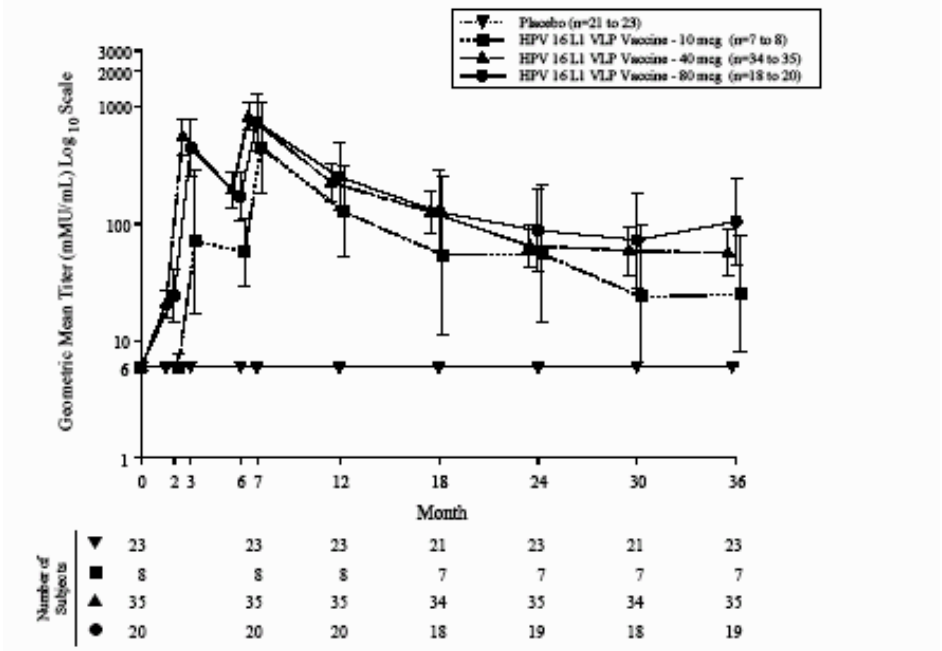
Treatment group	n	Observed Percentage of Subjects with HPV 16 Serum RIA Levels ≥ 20 mMU/mL at Month 7	95% CI for Percentage	p-value
Placebo (N=27)	23	**0.0% (0/23)**	0.0, 14.8%	1.000
HPV 16 L1 VLP 10/40 mcg (N=13)	8	**100% (8/8)**	63.1, 100%	Not done
HPV 16 L1 VLP 40 mcg (N=45)	35	**100% (35/35)**	90.0, 100%	<0.001
HPV 16 L1 VLP 80 mcg (N=24)	20	**100% (20/20)**	83.2, 100%	<0.001

N=Number of subjects vaccinated
n=Number of subjects contributing to analysis
Source: Table 24, CSR 002, p. 117

Secondary Immunogenicity Analysis

Atni-HPV 16 GMTs are shown by dose administered over time. All dose formulations elicited an immune response to anti-HPV 16, and GMTs persisted through Month 36 for all doses.

FIGURE 1
Protocol 002: HPV 16 Serum RIA GMTs and 95% CIs Through Month 36 (Per protocol population)



n = Number of subjects contributing to the analysis; HPV = Human papillomavirus; RIA = Radioimmunoassay; GMT = Geometric mean titer; VLP = Virus-like particle; mMU = Milli-Merck unit.

Vaccine and placebo were administered at 0, 2, and 6 months.

Source: Figure 2, CSR 002, p. 134

HPV 16 Infection: Two (2) of the subjects in the all HPV 16 Naïve Subject population experienced an HPV type 16 infection. Both subjects were in the placebo group.
Infection With HPV 6, 11, or 18: The incidences of HPV 6, 11, and 18 infection were generally comparable between treatment groups in both the HPV-naïve (Day 0 to Month 7) and Day 0 HPV-naïve populations. (Source: Table 33, CSR 002, p. 153-4, not shown here)

Safety Evaluation

- All 109 subjects had follow-up.
- Overall, the proportions of subjects who reported a clinical adverse event following any vaccination were generally comparable among treatment groups. (Note: The number of subjects in each treatment group is relatively small).
- There was no discernible difference in safety profile after doses 1, 2 and 3. (Source: Tables 68, 69, 70, CSR 002, p. 246-50, not shown here)
- In all treatment groups, the majority of adverse events were reported as being mild or moderate, and these rates were generally comparable among treatment groups. (Source: Table 71, CSR 002, p. 252, not shown here)

SAEs: none

Deaths: none

Injection site adverse experiences:

- The most common injection site adverse experience was pain/tenderness/soreness. (Source: Table 36, CSR 002, p. 163-4, not shown here)
- Overall, none of the injection site adverse experiences were of severe intensity, and most injection site adverse experiences were rated as mild in intensity. (Source: Table 37, CSR 002, p. 165, not shown here)
- Overall incidence rates in different dose groups -
  Placebo: 63.0% (17/27)
  10/40 mcg dose group: 46.2% (6/13)
  40 mcg dose group: 77.8% (35/45)
  80 mcg dose group: 70.8% (17/24)

Systemic clinical adverse experiences were generally comparable across treatment groups.

- Overall incidence rates in different dose groups -
  Placebo group: 96.3% (26/27)
  10/40 mcg dose group: 92.3% (12/13)
  40 mcg dose group: 82.2% (37/45)
  80 mcg dose group: 91.7% (22/24)
- The most common systemic clinical adverse experience was **headache:**
  Placebo: 70.4% (19/27)
  10/40 mcg dose group: 76.9% (10/13)
  40 mcg dose group: 64.4% (29/45)
  80 mcg dose group: 54.2% (13/24) (Source: Table 40, CSR 002, p. 169-73, not shown here)

- The percentages of systemic clinical adverse experiences that were reported as severe were comparable across treatment groups (range, 11.7 to 16.5%). (Source: Table 41, CSR 002, p. 174)

Conclusions for Protocol 002: The 40 mcg and 80 mcg doses of the HPV 16 L1 VLP vaccine appear immunogenic. The immune responses to all doses of the vaccine lasted for at least 36 months. No safety issues were identified from this Phase I trial.

Protocol 004: A Study of the Immunogenicity of Pilot Manufacturing Material of HPV 16 Virus Like Particle (VLP) Vaccine in 18-25 year old Women
Study Period: 10/12/98-9/30/01

Objective: To determine the safety of 3 doses (Month 0, 2, and 6) of pilot manufacturing material of HPV 16 VLP vaccine in subjects who are either HPV 16 seronegative or seropositive prior to vaccination. In addition, the antibody response levels for 4 doses of the vaccine were assessed (10, 20, 40 and 80 mcg).

Design: Phase IIa, randomized, double blind, placebo controlled, multicenter study.

Duration: Subjects to be followed for 14 days after each vaccination (last dose at Month 6). Subjects were followed for persistence of anti-HPV antibody through Month 24.

TABLE 16
Protocol 004: Treatment Plan

Dosage Level (Vaccine/Placebo)	Sample Size	Dosage Schedule
HPV 16 L1 VLP 10 mcg/0.5 mL	112	0, 2, 6 months
HPV 16 L1 VLP 20 mcg/0.5 mL	105	0, 2, 6 months
HPV 16 L1 VLP 40 mcg/0.5 mL	104	0, 2, 6 months
HPV 16 L1 VLP 80 mcg/0.5 mL	107	0, 2, 6 months
Placebo	52	0, 2, 6 months
Total	480	

Source: Table 2, CSR 004, p. 48 and Table 6, CSR 004, p. 80

Vaccine Products Used:
These were pilot manufacturing materials.
10 mcg/0.5 mL HPV 16 L1 VLP vaccine - V501 HSS009D001
20 mcg/0.5 mL HPV 16 L1 VLP vaccine – V501 HSS009H001
40 mcg/0.5 mL HPV 16 L1 VLP vaccine – V501 HSS009C001
80 mcg/0.5 mL HPV 16 L1 VLP vaccine – V501 HSS009B001
Placebo – PV501 HSS009A001 (225 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS)
Each dose of the vaccine contained 225 mcg AAHS.

Population: The study was conducted at 15 centers in the U.S.
Healthy females 16-23 years of age. These subjects were not screened for HPV 16 disease prior to enrollment.

Vaccination Schedule: Subjects received vaccine or placebo (0.5 mL) at 0, 2 and 6 months by IM injection in the deltoid.

Primary variable for immunogenicity was the proportion of subjects achieving anti-HPV 16 serum cRIA levels $\geq$ 20 mMU/mL 4 weeks postdose 3 (Month 7).
Secondary immunogenicity parameters included, e.g., anti-HPV 16 serum cRIA GMTs at 4 weeks postdose 3.

Primary variables for safety were the occurrence of any severe local injection site reactions and the incidence of any serious vaccine related adverse events.
The subjects also completed a VRC for local injection site reactions and oral Temperature for 5 days after vaccination and 14 days for systemic AEs after vaccination.

Efficacy: There were no efficacy endpoints.

Protocol 004 Surveillance:

TABLE 17
Protocol 004: Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Randomization Day 0	Mo 2	Mo 3	Mo 6	Mo 7	Mo 12	Mo 18	Mo 24
Lab:								
Pregnancy test (a)	+	+		+				
Serum Ab								
RIA	+		+		+	+	+	+
------- -----	+		(+)		(+)	+	(+)	(+)
Neutralization test	(+)		(+)		(+)	(+)	(+)	(+)
Serum for anti-HPV 16 assay development					+			
Blood for --- assay	+				+	+		
Vaccination (b)	+	+		+				
Clin f/u for safety	+	+	+	+	+			

(+) optional test as per Sponsor
a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)
b. Temp, wt. prior to each vaccination
c. Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. Phone calls at Day 14 after 1st injection to review all AEs and SAEs. At Months 2, 3, and 7, the study personnel together with the participant will review the VRC. At Months 2, 3, 6, and 7, subjects will be solicited for any gyn health concerns and any SAEs.
Source: Table 1, CSR 004, p. 44

Populations Analyzed
The **per-protocol population** was used in the primary analysis, and included subjects who received 3 doses of vaccine and were not protocol violators, and had serology at correct time points and after the 3rd dose of vaccine. As per Protocol 007-06, these subjects were seronegative at baseline.

All HPV 16-Naïve Subjects With Serology Data: Includes all subjects who were anti-HPV 16 cRIA seronegative or Serum ---------- negative at Day 0 and were free of detectable HPV 16 DNA (PCR) at Day 0 through Month 7, but could be protocol violators.

Results

Population (all study groups):

- A total of 480 healthy females, 18-26 years if age, were enrolled in the study.
- 384 subjects (80.0% of those enrolled), completed the vaccination phase. The majority of subjects who discontinued from the study were lost to follow-up, with the second most common reason refusal to participate further.
- Median age: 22 years.
- Distribution of ethnic groups: 82.3% Caucasian, 11% African American, 2.9% Asian and 2.3% Hispanic. (Source: Table 9, CSR 004, p. 87, not shown here)
- The percentage of subjects with a previous abnormal Pap smear was 1.3%.
- The percentage of those with a history of genital warts was 0.4%.
- The percentage of subjects with a history of any cervicovaginal infection was 1.0%. (Source: Table 10, CSR 004, p. 88, not shown here)

All dose levels elicited acceptable immune responses, defined as the proportion of subjects with anti-HPV 16 GMTs $\geq$ 20 mMU/mL at week 4 after dose 3. (See Table 18 below and Figure 2 below).

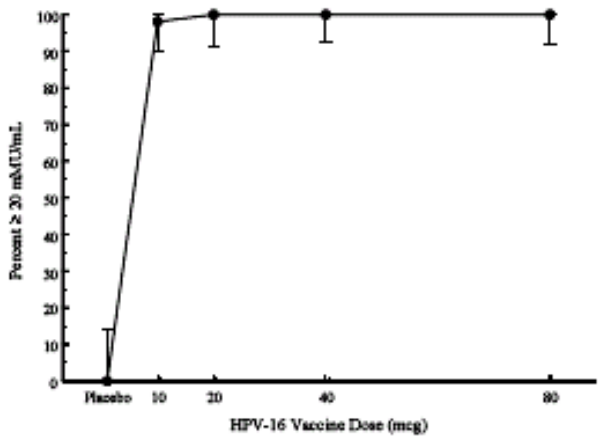
TABLE 18

Protocol 004: Immunogenicity Summary of Anti-HPV 16 Serum cRIA Levels $\geq$ 20 mMU/mL and GMTs Following Administration of Placebo or HPV 16 L1 VLP Vaccine (Per Protocol population – initially HPV 16 seronegative)

Treatment Group	Time Point	n	**Percentage of Subjects with Serum HPV 16 RIA Levels $\geq$ 20 mMU/mL**	95% CI	**GMT mMU/mL**	95% CI	p-value
Placebo (N=52)	Month 7	24	**0% (0/24)**	0.0, 14.2%	**< 6.0**	<6.0, < 6.0	N/A
HPV 16 L1 VLP 10 mcg (N=112)	Month 7	52	**98.1% (51/52)**	89.7, 100%	**981.6**	680.8, 1415.2	<0.001
HPV 16 L1 VLP 20 mcg (N=105)	Month 7	40	**100% (40/40)**	91.2, 100%	**2045.2**	1444.6, 2895.4	<0.001
HPV 16 L1 VLP 40 mcg (N=104)	Month 7	46	**100% (46/46)**	92.3, 100%	**1790.4**	1384, 2346	<0.001
HPV 16 L1 VLP 80 mcg (N=107)	Month 7	45	**100% (45/45)**	92.1, 100%	**2109.0**	1584.3, 2807.4	<0.001

N=Number vaccinated
n=Number evaluable
Source: Table 16, CSR 004, p. 99, and Table 18, CSR 004, p. 105

FIGURE 2
Protocol 004: Plot of Percentage of Subjects with Anti-HPV 16 Serum cRIA Levels ≥ 20 mMU/mL at 4 weeks postdose 3 and 95% CIs by Vaccination Group (Per Protocol Population)



	Vaccination Group				
		HPV 16 L1 VLP Vaccine			
	Placebo	10 mcg	20 mcg	40 mcg	80 mcg
Number of Subjects:	24	52	40	46	45

HPV = Human papillomavirus; VLP = Virus-like particles; cRIA = Competitive radioimmunoassay; mMU/mL = Milli-Merck unti per milliliter.

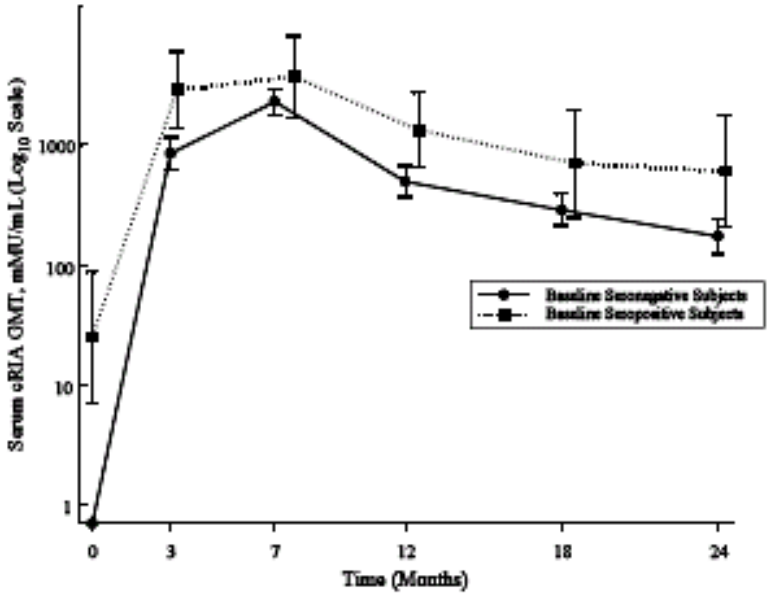
Source: Figure 1, CSR 004, p. 102

Dose Response at Months 12, 18 and 24:
There was a significant statistical difference in immune response ($p<0.001$) between the lowest dose (10 mcg) and placebo. This was true for the per protocol and all HPV 16 naïve with serology populations. (Source: Figure 8, CSR 004, p. 119, and Figure 26, CSR 004, p. 246, not shown here)

The **baseline seropositive subjects** had anti-HPV 16 cRIA levels at Month 7 that were 1.1 to 2.4 fold higher than those in the all HPV 16 naïve with serology in the active vaccine groups. The baseline seropositive subjects had anti-HPV 16 cRIA levels at Month 24 that were 2.4 – 3.5 fold higher than those in the all HPV 16 naïve with serology group in the active vaccine groups. (See Figure 3 below).

FIGURE 3

Protocol 004: Plot of anti-HPV 16 Serum cRIA GMTs (mMU/mL) and 95% CI in Baseline Seronegative and Seropositive Subjects who Received the 40 mcg Dose of Vaccine (Subjects who completed the Month 24 Visit Only)



Baseline Serostatus	Time (Months)					
	0	3	7	12	18	24
Seronegative	43	43	42	43	35	43
Seropositive	14	14	14	14	10	14

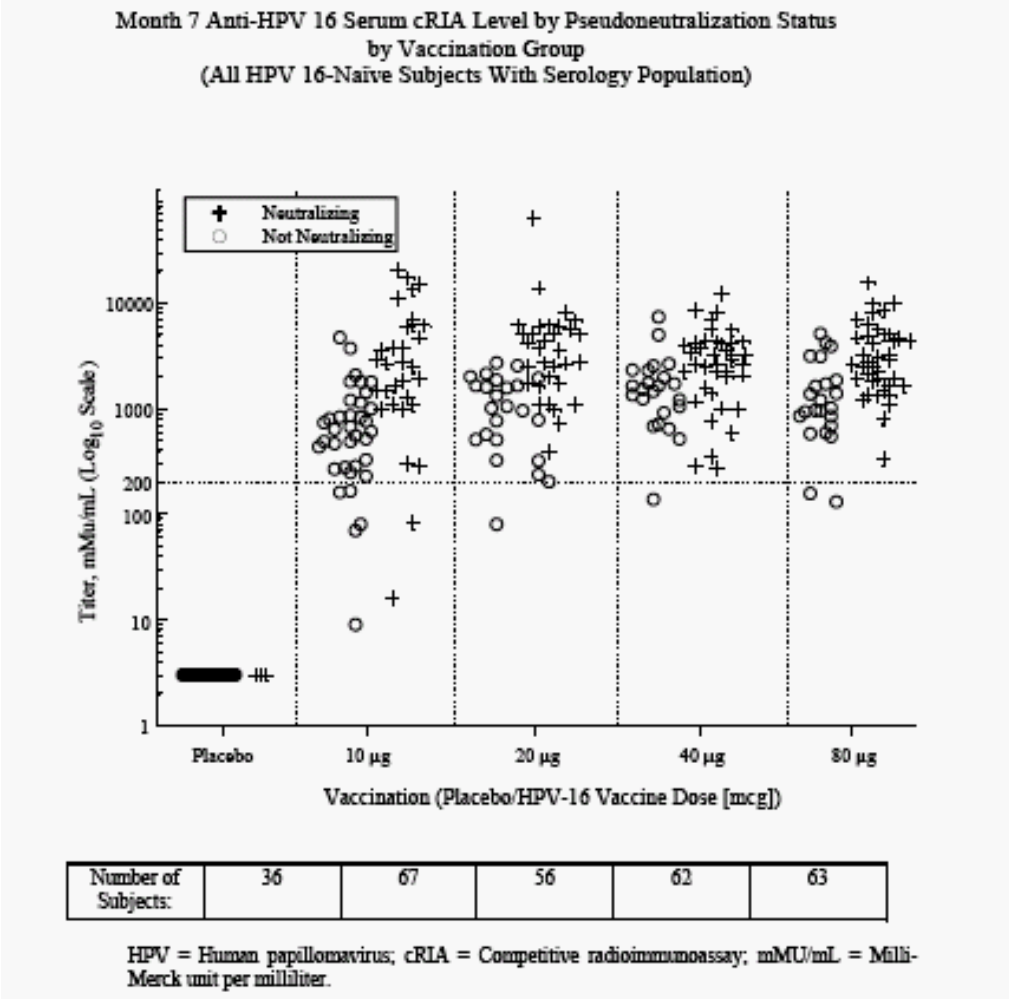
cRIA = Competitive radioimmunoassay; GMT = Geometric mean titer; mMU/mL = Milli-Merck unit per milliliter.

Source: Figure 31, CSR 004, p. 263

Correlation between anti-HPV 16 serum cRIA levels and pseudoneutralization responses at Month 7:

The correlation at Month 7 was moderate for this value (Kendall's tau=0.457).

FIGURE 4



Source: Figure 10, CSR 004, p. 132

Safety Evaluation

- Of the 480 subjects enrolled, 112 subjects received the 10 mcg dose, 105 subjects received the 20 mcg dose, 104 subjects received the 40 mcg dose, and 107 subjects received the 80 mcg dose 52 subjects received placebo.
- One subject (AN0328) in the placebo group discontinued due to an adverse event (headache).
- The majority of these adverse events were graded as mild to moderate in severity, and were generally comparable across dose groups. (Source: Table 77, CSR 004, p. 290, not shown here)
- There was no clear correlation with increasing dose and percentage with severe AEs. (Source: Table 78, CSR 004, p. 291, not shown here)
- **Grading of adverse events by baseline serostatus**: In the 10 mcg and 40 mcg dose groups, the percentages of baseline seropositive subjects reporting severe adverse events (31.0%, 19.2%, respectively) were higher than the percentages of baseline seronegative subjects reporting severe adverse events (14.5%, 7.7%, respectively). There was no clear dose response. (Source: Tables 79 and 80, CSR 004, p. 292-3, not shown here)

Injection site AEs:

- The most common injection site adverse event was pain/tenderness/soreness, with rates ranging from 79.4% in the 10 mcg group to 87.8% in the 40 mcg group. (Source: Table 26, CSR 004, p. 142, not shown here)
- The incidence of injection site adverse events was generally comparable for all doses, and there was no clear dose response. (Source: Tables 81, 82, 83, CSR 004, p. 294-7, not shown here)
- The incidence of injection site adverse events was generally comparable for those initially seronegative and those initially seropositive, and comparable across different doses. (Source: CSR 004, Tables 27, 28 [p. 144-5]; Tables 84, 85, 86, 87, 88, 89 [p. 298-303]), not shown here.
- Most of the injection site adverse events were rated as mild to moderate, and the distributions across dose groups were comparable. (Source: Table 29, CSR 004, p. 147, not shown here)

Systemic adverse events

- The overall incidences of systemic adverse events from Days 0-14 were generally comparable in all 5 groups (with incidences ranging from 68.3% - 78.5%).
- The incidence of fever Days 0-14 was somewhat higher in vaccine groups as compared to the placebo group (with 6.7% with a fever in the 80 mcg dose group and 2.0% in the placebo group).
- The most common clinical adverse event was headache, present in 48% of placebo recipients and in 46.9 to 49.5% of vaccine recipients. (Source: Table 35, CSR 004, p. 157-63, not shown here)
- The incidences of systemic adverse events were similar for those initially seronegative and those initially seropositive and these adverse events were generally comparable for the different doses of vaccine.
- The majority of systemic adverse events were rated as mild to moderate. (Source: Tables 38-39, CSR 004, p. 167-8, not shown here)
- The rates of most of the specific systemic adverse events appeared comparable between the vaccine and placebo groups.

Serious Adverse Events: (3)

- **AN 00418 (10 mcg dose)** was hospitalized for **gastroenteritis** at Day 8 after dose 2. She was given IV fluids overnight and then discharged. She recovered, and received the third dose of vaccine.
- **AN 00819 (80 mcg dose)** was hospitalized for a **suicide attempt** 24 days after Dose 2. Hospitalized for 2 days. She went onto receive the third dose of vaccine.
- **AN 00747 (40 mcg dose)** was hospitalized for **severe pneumonia** 49 days after Dose 2. Hospitalized for 2 days. This subject subsequently received the 3rd dose of vaccine.

Deaths: none

Impact of Vaccination on Pregnancy Outcomes: All pregnancies occurring through Month 7 were followed for outcome. There were 2 pregnancies in the placebo group, and 17 pregnancies in the vaccine group.

- **Vaccine group:** 17 pregnancies: there were two miscarriages, 4 termination of pregnancies, 8 healthy infants, 1 infant with a congenital anomaly (tracheomalacia), and 2 with unknown outcomes.
  - **Two Miscarriages: AN 00079** received dose 1 of 80 mcg vaccine, and 2.5 months later, was noted to be pregnant. Approximately 3 months after vaccination, this subject miscarried (discontinued from study). **AN 00669** received 1 dose of 20 mcg vaccine, and 2 months later was noted to be pregnant. She miscarried at 3 months after vaccination.
  - Four **termination of pregnancies** (AN 00331, 00635, 00830, 00906).
  - Eight **healthy infants:** (AN 00118, 00337, 0627, 00664, 00816, 00902, 00910, 00925).
  - One infant with **congenital anomaly**: AN 00350 received the first 2 doses of 10 mcg vaccine on 5/12/99 and 7/15/99. The subject became pregnant (app. 1 month post-vaccination), and delivered a male infant on -------. On 6/21/00, non-specific respiratory abnormalities were noted in the newborn, who was diagnosed with tracheomalacia.
  - Two subjects who became pregnant were **lost to follow-up**: (AN 00301 and 00930)
- **Placebo group:** The two placebo recipients delivered healthy babies. (AN 00122 and AN 00920)

Conclusions for Protocol 004: All HPV 16 L1 VLP active vaccine dose levels studied were immunogenic. Anti-HPV 16 serum cRIA responses decline following completion of the vaccination regimen; however, at 18 months Postdose 3, anti-HPV 16 levels were detectable in the majority of vaccinees and anti-HPV 16 GMTs remained numerically higher than those in women who developed anti-HPV 16 responses to natural infection. In baseline anti-HPV 16 seropositive subjects, anti-HPV 16 responses to the HPV 16 L1 VLP vaccine appear numerically higher than those in baseline seronegative subjects at Month 3, Month 7, and in the persistence phase (through Month 24). There was no specific safety concern identified. There was one subject who received 2 doses of the 10 mcg dose vaccine, and became pregnant app. 1 month after the second vaccination. Her child had a congenital anomaly, tracheomalacia. (See discussion in safety conclusion regarding the overall rate of congenital anomalies across the phase 3 trials).

Protocol 006: A Study of the Safety/Tolerability and Immunogenicity of <u>HPV 18</u> Virus Like Particle (VLP) Monovalent Vaccine in 16-23 year old Women
Study Period: 3/2/00 – 1/25/01

Objective: To evaluate the safety and tolerability of three doses of the the HPV 18 L1 VLP vaccine in women (0, 2 and 6 months), and to assess the immunogenicity of the vaccine in HPV 18 seronegative and PCR negative women.
In addition, to obtain preliminary safety experience with the vaccine in women who are positive for HPV 18 (either by serology and/or DNA status).

Design: Phase I, double blind, placebo controlled (alum control), randomized, multicenter trial. All subjects, investigators and their staff, and laboratory personnel were blinded to treatment group.

TABLE 19
Protocol 006: Treatment Plan and Vaccination Schedule

Group	Treatment	Dosage Schedule	Dose Volume Administered
A	HPV 18 L1 VLP Vaccine (80 mcg)	Day 0 Month 2 Month 6	0.5 mL
B	Placebo	Day 0 Month 2 Month 6	0.5 mL

HPV = Human papillomavirus. VLP = Virus-like particles.

Source: Table 2, CSR 006, p. 36

Vaccine Products Used
The lots used contained final development process material.
80 mcg/0.5 mL HPV 18 L1 VLP Vaccine – V501 VAI012B002
Placebo- V501 VAI012A002 (450 mcg aluminum as amorphous aluminum hydroxide sulfate or AAHS)
The vaccine contains 450 mcg AAHS as adjuvant.

Population: The study was conducted at 3 centers in the U.S.
The subjects were healthy 16-23 year old females who did not have a history of prior Pap test abnormalities.

Primary variable of interest for immunogenicity was the proportion of subjects achieving an anti-HPV 18 serum cRIA level $\geq$ 200 mMU/mL Postdose 3 (Month 7).

Safety Parameters: The primary variables of interest for safety/tolerability were the occurrence, if any, of severe, local injection-site reactions and the incidence of any serious vaccine-related adverse experiences.

Efficacy Parameters: Protocol 006 was not designed as an efficacy study; however, the study was designed to collect specimens that could be used to evaluate vaccine efficacy.
Incident HPV 18 infection rates: defined as detection of HPV 18 DNA by the type-specific HPV 18 PCR assay in cervicovaginal specimens obtained at Month 7 in women who were HPV 18 naïve at enrollment.
Clinical HPV disease: defined as the development of new HPV-related Pap test abnormalities (ASCUS or worse) and Cervical Intraepithelial Neoplasia (CIN) detected in biopsy specimens in subjects who had a negative Pap test at enrollment.

TABLE 20

Protocol 006: Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Randomization Day 0	Mo 2	Mo 3	Mo 6	Mo 7
Gyn history and exam	+				+
Lab:	+				+
Pregnancy test	+	+		+	
Urine PCR or LCR for GC	+				+
Urine PCR or LCR for chlamydia	+				+
Serum Ab					
HPV 18 EIA/cRIA assay development					+
HPV 18 cRIA	+	+	+	+	+
---------- swabs for HPV PCR	+				+
Swab for HSV culture (if indicated)	+				+
Ph Vag fluid	+				+
Wet mount/trich/BV	+				+
Whiff test BV	+				+
KOH for yeast (if indicated)	+				+
---------- swab for HPV PCR	+				+
---------- swab for HPV PCR	+				+
Pap test (Thin Prep) cyto			+		+
Vaccination (b)	+	+		+	
Clin f/u for safety	+	+	+	+	+

Any test may have been repeated if medically indicated.

Source: Table 1, CSR 006, p. 30

Safety assessments:

- The primary endpoints for safety were the incidences of serious vaccine-related adverse experiences and severe injection-site reactions.
- For the injection-site reactions of redness and swelling, a size of “more than 2 inches” was considered severe.
- To address specific adverse experiences, the incidences of injection-site adverse experiences Days 0 to 14 or specific systemic adverse experiences within 14 days postvaccination were tabulated for both the treatment groups.
- Risk differences between recipients of the HPV 18 L1 VLP vaccine and recipients of the placebo were estimated and their 95% two-sided confidence intervals were provided.
- Pregnancies that occurred during the study were reported and the outcomes were listed.

Populations Analyzed

The **per-protocol population** was used in the primary analysis. The per-protocol population **excluded** protocol violators, subjects who were not HPV 18-naïve at enrollment, and subjects who acquired HPV 18 infection during the vaccination regimen.

The **Population of All HPV 18-Naïve Subjects With Serology Data:** The population of all HPV 18-naïve subjects with serology data includes all subjects who were anti-HPV 18 cRIA seronegative at Day 0 and were free of detectable HPV 18 DNA (PCR) at Day 0 and Month 7. This approach includes general protocol violators.

Results

Population (all study groups):

- A total of 40 women 17-23 years of age were enrolled in this study at three clinical sites.
- There were 27 subjects in the vaccine group and 13 in the placebo group.
- 25 (92.6%) in the vaccine group and 12 (92.3%) in the placebo group completed the study. One subject in the vaccine group refused further participation (AN 00024) and one was lost to follow-up (AN 00032). In the placebo group, the one subject discontinued due to an adverse event. This subject experienced moderate hives on Days 2 and 3 after the first dose of vaccine.
- Mean age: 20.7 years.
- Ethnic Distribution: Caucasian (80%); 5% each Asian, Hispanic and other; 2.5% Black and Native American. (Source: Table 8, CSR 006, p. 70, not shown here)

Immunogenicity Results

Primary Immunogenicity Endpoint:

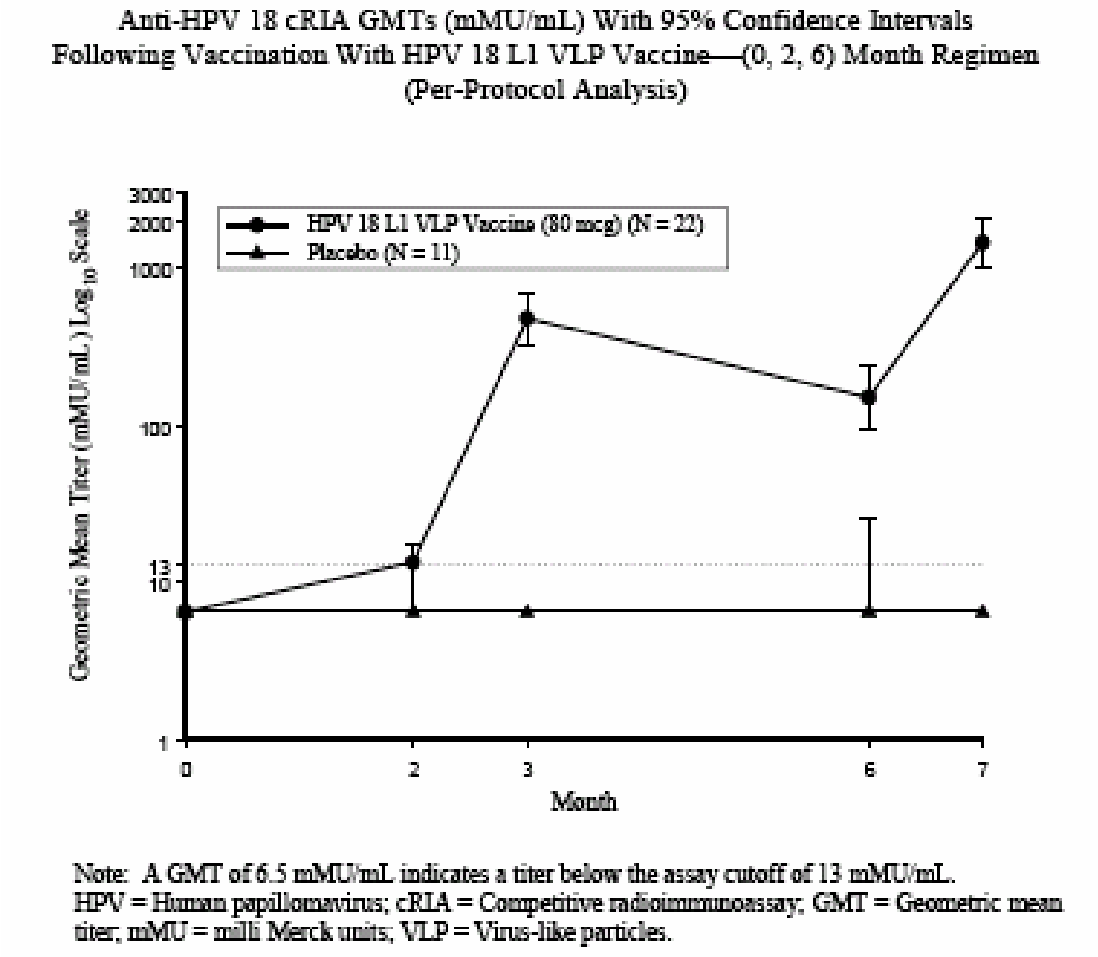
There was significant statistical evidence to support that the HPV 18 L1 VLP vaccine induced acceptable immune response in the per protocol population. The proportion of subjects achieving an anti-HPV 18 serum RIA level $\geq$ 200 mMU/mL by Week 4 postbooster in the HPV 18 L1 VLP vaccine group was 100% (22/22) [95% confidence interval: 84.6%, 100.0%].

TABLE 21
Protocol 006: Immunogenicity Summary of Anti-HPV 18 Serum cRIA Responses to HPV 18 L1 VLP Vaccine in Initially Seronegative Subjects (Per Protocol Population)

Treatment Group	Timepoint	N	**Percentage of Subjects with Anti-HPV 18 Serum cRIA level $\geq$ 200 mMU/mL**	95% CI	**GMT mMU/mL**	95% CI
HPV 18 L1 VLP 80 mcg (N=27)	Month 7	22	**100% (22/22)**	84.6, 100%	**1448.3**	1004, 2089.4
Placebo (N=13)	Month 7	11	**0.0% (0/11)**	0.0, 28.5%	**< 13.0**	<13.0, < 13.0

Source: Table 16, CSR 006, p. 82

FIGURE 5
Protocol 006: Anti-HPV 18 cRIA GMTs with 95% CIs Following Vaccination with HPV 18 L1 VLP Vaccine (Per Protocol Population)



Note: A GMT of 6.5 mMU/mL indicates a titer below the assay cutoff of 13 mMU/mL.
HPV = Human papillomavirus; cRIA = Competitive radioimmunoassay; GMT = Geometric mean titer; mMU = milli Merck units; VLP = Virus-like particles.

Source: Figure 1, CSR 006, p. 84

HPV Infection:
No subjects who were initially HPV 18 PCR negative at Day 0 became HPV 18 PCR positive at Month 7.

Safety Evaluation:
- All subjects were followed for adverse events for 15 days (days 0-14) after each vaccination.
- The proportions of subjects reporting a clinical adverse event were comparable between treatment groups following each vaccination visit. (Source: Table 36, 37 and 38, CSR 006, pp. 122-4, not shown here)
- Most of the AEs were mild in severity.
- The placebo group had a higher frequency of reports of severe adverse events (9.9% for the placebo group compared with 2.7% for the vaccine group). (Source: Table 45, CSR 006, p. 132, not shown here).
- More subjects in the vaccine group reported an AE with a maximum intensity of moderate (48.1%) compared to the placebo group (38.5%), but there was a higher

frequency of subjects in the placebo group reporting a maximum AE of severe grade (30.8%) compared to the vaccine group (14.8%). (Source: Table 46, CSR 006, p. 132, not shown here)

Injection Site Adverse Event

- Higher in vaccine recipients (96.3%) compared to the placebo group (84.6%).
- The most common injection site AE was pain/tenderness/soreness (96.3% in the vaccine group and 84.6% in the placebo group). (Source: Table 24, CSR 006, p. 96, not shown here)
- The majority of adverse events were rated as mild for all solicited adverse events. (Source: Table 26, CSR 006, p. 98)

Systemic Adverse Events

- The proportions were comparable across treatment groups.
- Overall, 70.4% and 84.6% of subjects in the vaccine and placebo groups, respectively, reported a systemic AE in the 14 days after any vaccination.
- The 2 most common systemic AEs were headache (48.1% and 61.5%, in the vaccine and placebo groups, respectively), and pharyngitis (7.4% and 30.8% in the vaccine and placebo groups, respectively). (Source: Table 28, CSR 006, p. 100-2, not shown here)
- Most of the systemic AEs in both groups were mild to moderate in severity. (Source: Table 29, CSR 006, p. 102, not shown here)

SAEs: none

Discontinuations due to AE: One subject in the placebo group discontinued due to hives, moderate in intensity, at Day 2 and 3 postdose 1.

Deaths: none

Pregnancies:
One subject **(AN 00003),** a 20 year old subject, was noted to have a positive pregnancy test 14 days after the 3rd dose of HPV 18 L1 80 mcg vaccine. The subject had a spontaneous miscarriage at 6 weeks after the LMP, or 18 days after the last dose of vaccine. This was considered an adverse event of special interest.

Conclusions for Protocol 006: Three doses (at Month 0, 2, and 6) of 80 mcg dose of the HPV 18 L1 VLP vaccine adjuvanted with 450 mcg AAHS was noted to be immunogenic at 4 weeks postdose 3. The GMTs of anti-HPV antibodies were highest at 1 month after the 3rd dose of vaccine. There was a higher proportion of subjects in the vaccine group with injection site reactions compared to the placebo group, although only the proportion with erythema was shown to be statistically higher. Most of the injection site AEs were mild in intensity, although the vaccine group had a higher reporting frequency of moderate injection site AEs as compared to the placebo group. There was no discernible difference in the proportion of subjects with systemic adverse events in the vaccine group as compared to the placebo group, and the placebo group had a higher frequency of

reports of moderate intensity systemic AEs. There was one miscarriage at 18 days after the 3rd dose of vaccine.

Reviewer's Comment: The immune response and safety results from Protocols 001, 002, 004, and 006 provided support for continued development of the quadrivalent HPV vaccine.

5.4 Regulatory Background Information

TABLE 22
Regulatory Background Information

Date	Action
2000	Submission of Original Submission
11/01	VRBPAC meeting to discuss Endpoints for Phase 3 trials
7/01	End of Phase 2 meeting
5/05	Pre-BLA Meeting
8/05	Submission of first part of rolling BLA
12/05	Submission of final part of rolling BLA
5/18/06	VRBPAC meeting
6/8/06	BLA Approval

All clinical studies submitted to the BLA were conducted under IND. Studies were reviewed and found to be safe to proceed. Studies that enrolled pediatric subjects included Parent/Guardian consent as well as subject assent.

6 Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Material Reviewed

BLA 125126 contained the sponsor's clinical study reports.

6.2 Tables of Clinical Studies

TABLE 23
Phase I-II studies with Monovalent HPV VLP Vaccines

Study Protocol	Description	Study Population	Enrolled Subjects	Vaccine: Placebo	Dosing Vaccine	Placebo	Dates
001-09: Multicenter (sites in US) **HPV-11 VLP**	Phase 1 sequential dose escalating study HPV-11 – safety and immunogenicity	18-25 yo women	140	Alum 225: 28 10 mcg: 28 20 mcg: 28 50 mcg: 28 100 mcg: 28	3 doses @ 0, 2, 6 M	Alum @ 0, 2, 6 M	9/22/97-8/7/01
002-06: Single center (U of Washington) **HPV-16 VLP**	Phase 1 sequential dose escalating study HPV-16 – safety and immunogenicity	18-25 yo women	109	Alum 225: 27 10/40 mcg: 13 40 mcg: 45 80 mcg: 24	3 doses @ 0, 2, 6 M	Alum @ 0, 2, 6, M	1/5/98-10/31/01
004-06: Multicenter (15 sites in US) **HPV-16 VLP**	Phase 2a dose ranging study HPV 16 – safety and immunogenicity	18-26 yo women	480	Alum 225: 52 10 mcg: 112 20 mcg: 105 40 mcg: 104 80 mcg: 107	3 doses @ 0, 2, 6 M	Alum @ 0, 2, 6 M	10/12/98-9/30/01
006-Multicenter (3 sites in US) **HPV 18 VLP**	Phase 1 safety and immunogenicity	16-23 yo women	40	Alum 225: 13 80 mcg: 27	3 doses @ 0, 2, 6 M	Alum @ 0, 2, 6 M	3/2/00-1/25/01
005—05 Multicenter (16 sites in US) **HPV 16 VLP**	Phase 2a safety, immunogenicity, efficacy	16-25 yo women	2409	Alum 225: 1205 40 mcg: 1204	3 doses @ 0, 2, 6 M	Alum @ 0, 2, 6 M	10/22/98-3/31/04

TABLE 24
Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccine Summary of Pivotal Phase IIb-III Trials

Study Protocol	Description	Study Population	Planned Subjects	Vaccine: Placebo	Number of subject who received Gardasil	Dosing Vaccine	Placebo	Dates
007-06 Multicenter (23 sites in 5 countries: US, Brazil, Finland, Norway, Sweden)	Phase 2b + dose range (Part A and B)	16-23 yo women	Part A: 45 Part B: 1000	alum 225: 135, alum 450: 140 20/40/40/20: 276 40/40/40/40: 272 80/80/40/80: 280	276	3 doses @ 0,2,6,M	Alum @ 0,2,6,M	5/26/00 – 5/10/04
013-04 Multicenter (62 centers in 16 countries in North America, Latin America, Europe and Asia)	Phase 3 Efficcacy Internal and External Genital Disease	16-23 yo women	5700	2717:2725 +304 HPV16	2717	3 doses @ 0,2,6M	Alum @0,2,6M	12/28/01-7/15/05 (ongoing for additional follow-up)
011-03 Substudy of 013-04	P3 S+I Hep B coadministration	16-23 yo women	(1800)	(HPV+HPB: 466 HPV +HPP: 468 HPVP+ HBV: 467 HPVP+HBP: 465)	(934)	3 doses @ 0,2,6M HepB @ 0,2,6M	Alum @0,2,6M HepB placebo at same timepoints	12/28/01-6/11/04
012-03 Substudy of 013-04	Phase 3 Safety + Immunogenicity Bridge to HPV16	16-23 yo women	(3900)	(1783:1788) 304 HPV16 bridge	(1783)	3 doses @ 0,2,6M	Alum @0,2,6M	5/30/02-6/30/04
015-04 Multicenter (90 centers in 14 countries in 4 geographic areas)	Phase 3 Safety +Immunogenicity+Efficacy Consistency Lot substudy NSAE substudy Long-term follow-up study	16-23 yo women (16-26 yo in Singapore)	11500	6082:6075 (459:457 NSAE) (1514:1513 consistency lot) (uncertain number in long term)	6082	3 doses @ 0,2,6M	Alum @0,2,6M	6/24/02-6/10/05 (ongoing for additional follow-up)
016-03 Multicenter (61 centers in 19 countries in 4 geographic areas)	Phase 3 Safety + Immunogenicity End expiry substudy	9-15 yo girls 9-15 yo boys 16-23 yo women	3000	No Placebo Full dose: 506 girls, 508 boys, 511 women 60% dose: 508 girls and women 40% dose: 513 girls and women 20% dose: 503 girls and women	1529 total 1019 females	3 doses @0,2,6M	No placebo	12/7/02-9/20/04
018 Multicenter (47 sites in 10 countries)	Phase 3 Safety + Immunogenicity	9-15 yo girls and boys	1650	1179:596	1775 (615 girls 564 boys)	3 doses @ 0,2,6M	Saline @ 0,2,6M	10/8/03-1/19/05

N: number of subjects who received at least one dose of 20/40/40/20 dose vaccine

Complete study reports from 12 clinical trials were provided in the BLA. Furthermore, the applicant submitted integrated summary reports of safety, efficacy, and immunogenicity that included various studies (for example, integrated efficacy of studies 005, 007, 013, and 015; summary of safety for 005, 007, 013, 015, 016, and 018). Overall, approximately 60,000 pages of clinical review materials were

submitted electronically for review. The review was completed in a six-month regulatory time frame.

6.3 Review Strategy

The individual clinical study reports were initially reviewed (Phase I, II, and III), followed by review of SAS datasets with JMP software. The summary of clinical efficacy (cervical lesions, external genital lesions), the summary of safety, and the integrated analysis of efficacy were also reviewed. Separate reports for congenital anomalies and pathology panel were also reviewed. In addition, requests for additional analyses were made in several communications (see licensing package for all telecons and dates) and the responses from the sponsor were reviewed as well.

6.4 Good Clinical Practice and Data Integrity – See BIMO review by Mr. Robert Wesley.

One investigator in Sweden drew extra blood from subjects for use outside the study, and he was removed as an investigator from the study. The data from his site were reviewed by the sponsor and no compromise of data integrity was reported.

One laboratory technician had deviated from an SOP when testing serum samples from trials of Gardasil. An evaluation of the extent of this deviation revealed that 2.6% of sera in the Phase III trials of Gardasil may not have conformed to the SOP. The sponsor retested non-conformant Day 1 results from the efficacy protocols Protocol 007, 013, and 015 for the per protocol and MITT-2 populations because serostatus was included in assessment of eligibility for analysis in the per protocol and MITT-2 populations. The results for the MITT-3 population did not change because subjects were included in this population regardless of baseline serostatus. Re-analysis of anti-HPV levels and seroconversion rates were compared to those provided in the original BLA for the vaccine for efficacy analyses. There was no difference in the majority of these analyses. When there were any differences, these involved tenths of a point difference for either the 95% CIs or the observed efficacy, which did not affect the licensure decision.

6.5 Financial Disclosures –

There were 2301 investigators involved in the trial.

The majority of the investigators (N=2172) were certified regarding an absence of financial arrangements. 116 investigators did not provide information (most of these investigators had left the site with which they were associated and could not be located.) 14 of the investigators had received payment from the sponsor. One of these investigators (----------) was involved in Protocol 005-003 [N=212], 007-003 [N=57], and 015-004 [N=231], and received the largest sum. His site was investigated by BIMO and no problems were identified (letter issued to investigator). The sponsor has indicated that they have not entered into any financial arrangement with any clinical investigators where the value of the compensation could be affected by the outcome of the study (21 CFR 54.2(a)). The sponsor also indicated that they conducted an internal search for all payments that met the definition of "significant payments of other sorts" (21 CFR 54.2(f)) and reported that

information. Significant payments of other sorts are calculated cumulatively when an investigator is involved in more than one protocol in a submission. These investigators are listed in sponsor's Table D-1. The sponsor indicates that bias has been minimized, when appropriate, through study design (e.g., double-blind, placebo controlled, multicenter study sites).
All study reports submitted to the BLA were considered "Covered clinical trials", (i.e., Protocol 001, 002, 004, 005, 007, 013 [which included substudies 011 and 012] 015, 016 and 018).

7 Human Immunogenicity

The vaccine was shown to be immunogenic for all 4 vaccine HPV types (HPV 6, 11, 16, 18) as measured by Merck's competitive Luminex immunoassay, which was used for Protocols 007, 013, 015, 016 and 018. An immune correlate of protection was not identified. In the Phase I studies, a competitive radioimmunoassay was used to measure anti-HPV 6, 11, 16, and 18 antibodies. Preclinical experiments were conducted to determine the minimal serum anti-HPV 11 level associated with 100% neutralization of a large dose of live HPV 11 virions in the ---------- xenograft model for HPV 11 infection. In African Green Monkeys (AGMs), a postvaccination level corresponding to human serum anti-HPV 11 serum RIA level of 20 to 50 mMU/mL was sufficient to cause 100% neutralization in this model. The immune response at 1 month after dose 3 of the vaccine was higher than that seen in subjects who were previously PCR positive and/or seropositive for that specific HPV subtype.

8 Clinical Studies

8.1: Trial #1

Protocol 015: A Randomized, Worldwide, Placebo Controlled, Double Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16/18 Related CIN 2/3 or Worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus Like Particle (VLP) Vaccine in 16-23 Year Old Women – The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)

Objective/Rationale

The **primary objectives** of the study were to evaluate **safety and efficacy** of Gardasil.

The **primary efficacy objective** was to demonstrate that the vaccine reduces the incidence of the composite endpoint of HPV 16- and HPV 18-related CIN 2, CIN 3, AIS, or cervical cancer in subjects who were naïve to the relevant HPV types at baseline. (Naïve to the relevant HPV type was defined as seronegative at Day 1 for the relevant HPV type and PCR negative for that HPV type at Day 1 through Month 7 for the same HPV type.) PCR testing was performed on the ---------- samples and ---------- samples.

A **secondary immunogenicity objective** was to evaluate the persistence of vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti- HPV 18 responses in subjects who were naïve to the relevant HPV types (naïve defined above).

Other **exploratory efficacy objectives** included:

- Assessment of the impact of Gardasil on the incidence of the composite endpoint of **ALL CIN 2/3** or invasive cervical carcinoma (caused by any vaccine or nonvaccine HPV type) in subjects who are PCR negative and seronegative at baseline and PCR negative through Month 7 for high-risk HPV types.
- Assessment of the impact of Gardasil on the incidence of the composite endpoint of HPV 6-/11/16-/18-related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), or Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer or vaginal cancer in subjects who are PCR negative and seronegative at baseline and PCR negative through Month 7 for the relevant HPV type(s).

The study included **three substudies**.

- The **Nonserious Adverse Experience Substudy** provided an assessment of the safety of the vaccine in a group subjects who completed a Vaccine Report Card (U.S. only).
- The **Consistency Lot Substudy** was intended primarily to demonstrate that the Final Manufacturing Process (FMP) results in vaccine that induces consistent serum anti-HPV 6, 11, 16, and 18 responses 4 weeks following dose 3, and to secondarily evaluate the persistence of these antibody levels out to 4 months following dose 3, Month 24 (completed), and subsequently Month 48.
- The **Registry Substudy** is planned to complete ascertainment of cytology and pathology specimens. The registry-based substudy is to be conducted in countries in which Cervical Screening Registries already exist. **The Registry substudy will be submitted in a separate CSR at the conclusion of this 4-year study.**

Design Overview: The study was a Phase III, large, randomized, placebo controlled, multicenter (90 centers worldwide), multinational efficacy study in app. 11,500 subjects.

- **Randomization:** Subjects were randomized in a 1:1 ratio to receive either quadrivalent HPV vaccine or placebo. For the consistency lot substudy, subjects were further randomized to receive 3 different lots of the vaccine in a 1:1:1 ratio (500 subjects per lot). Subjects enrolled in the Consistency Lot substudy received different lots of the vaccine than the other subjects in Protocol 015. Due to the timing of availability of the third lot for the consistency lot substudy, after approximately 8500 subjects were enrolled in the efficacy study, a second allocation schedule was generated which randomized the remaining 3000 subjects in the substudy in a 1:1:1:3 ratio to receive 1 of 3 consistency lots of vaccine or placebo.
- Table 24 below shows the timing of study procedures.

TABLE 25

Protocol 015: Schedule of Clinical Observations and Laboratory Measurements

Event	Randomization Day 1	Month 2	Month 6	Month 7	Month 12	Month 24	Month 36	Month 48
Gynecologic /medical history	X			X	X	X	X	X
Physical examination	X							
Gynecologic Exam	X			X	X	X	X	X
Urine for Chlamydia and Gonorrhea (a)	X				X	X	X	X
Herpes culture; vaginal fluid pH; saline wet mount for trichomonas and bacterial vaginosis; whiff test for bacterial vaginosis; and KOH testing for yeast	These tests were to be performed at the discretion of the investigator							
Testing for Gonorrhea, Chlamydia, hepB serology, hep C serology, and HIV	These tests were to be performed at the discretion of the investigator							
Blood for immune response (anti-HPV 6, 11, 16, 18 by cLIA)	X			X (b)		X (b)		X (b)
Genital swabs for PCR types	X			X		(X)	(X)	(X)
Pap testing	X			X	X	X	X	X
Pregnancy Tests	X	X	X					
Vaccination with Gardasil	X	X	X					

(a)PCR or LCR (Ligase Chain Reaction) or SDA (Strand Displacement Amplification) were mandatory, except in Denmark, Finland, Iceland, Norway, Poland, or Sweden.
(b)Consistency Lot Substudy: At the time of this report, blood tests available to Month 24 (app. 1.5 years after the third dose of Gardasil)
() Samples obtained, testing optional
Source: From Table 5-5, CSR 015v2, p. 91

Population: 11,500 healthy adult women 16-26 years of age were planned for enrollment. This study was conducted at 90 centers worldwide in Brazil, Colombia, Denmark, Finland, Iceland, Mexico, Norway, Peru, Poland, Singapore, Sweden, United Kingdom, and the US.

Inclusion and Exclusion Criteria – See Appendix 1

Products Mandated by Protocol

TABLE 26
Protocol 015: Clinical Products Used

Clinical Material	Formulation Lot Information	Dosage	Package
Initial Enrollment Period			
Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccines	V501 VAI018I001, V501 VAI025T001, V501 VAI025T002.	HPV 6, 11, 16, 18 L1 VLP 20/40/40/20 mcg with 225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
Placebo	PV501 VAI019A001	225 mcg aluminum adjuvant/0.5 mL	"
Consistency Lot Substudy			
Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccines Consistency Lot #1	V501 VAI020I001	HPV 6, 11, 16, 18 L1 VLP 20/40/40/20 mcg with 225 mcg aluminum adjuvant/0.5 mL	"
Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccines Consistency Lot #2	V501 VAI020I002	HPV 6, 11, 16, 18 L1 VLP 20/40/40/20 mcg with 225 mcg aluminum adjuvant/0.5 mL	"
Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccines Consistency Lot #3	V501 VAI025T003	HPV 6, 11, 16, 18 L1 VLP 20/40/40/20 mcg with 225 mcg aluminum adjuvant/0.5 mL	"
Placebo	PV501 VAI028P005	225 mcg aluminum adjuvant/0.5 mL	"

Source: From CSR Synopsis, CSR 015v2, p. 51

Endpoints

Efficacy Endpoints

Primary Efficacy Endpoint: The consensus diagnosis of the Pathology Panel of CIN 2, CIN 3, AIS, or cervical cancer associated with HPV 16 and/or HPV 18. The primary efficacy analysis included subjects who were HPV 16 naïve (for the HPV 16 related endpoints), and subjects who were HPV 18 naïve (for the HPV 18 related endpoints).

Secondary Efficacy Endpoint: The incidence of cervical biopsies and definitive therapies (e.g., LEEP, laser conization, and cold-knife conization) due to HPV 16- and HPV 18-related disease.

Exploratory Efficacy Endpoints:

- The incidence of all CIN 2/3 (regardless of causal HPV type) or invasive cervical carcinoma.
- The incidence of the composite endpoint of HPV 6-, HPV 11-, HPV 16-, and HPV 18-related external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer.
- The incidence of the composite endpoint of HPV 6-, HPV 11-, HPV 16-, and HPV 18-related CIN 1 or worse.
- The incidence of the composite endpoint of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer of any HPV type.

- The antibody responses in vaccine recipients who have breakthrough cases of HPV 6/11/16/18-related external genital warts, VIN, or VaIN or HPV 6-, 11-, 16-, or 18-related CIN or worse.
- Potential therapeutic effect was assessed in exploratory analyses.

Pathology Panel: The efficacy endpoints included histopathological diagnoses provided by a Pathology Panel. See **Appendix 2** for details. These lesions had to contain the relevant HPV type (i.e., 6, 11, 16, or 18) in order to be considered a case. The pathology panel consisted of 4 pathologists expert in the diagnosis of genital lesions. The panel members were blinded as to treatment arm and HPV PCR status, as well as to the diagnoses of other panel members. Slides were sent to 2 panel members independently. If there was agreement by these 2 panel members, that diagnosis became the study diagnosis for the material. If there was a discrepancy in diagnosis, the slides were sent to a third panel member (without indication that this 3rd panel member was the potential tie-breaker.) If the 3rd panel member agreed with one of the other readings, that diagnosis became the study diagnosis for that lesion. If there were 3 different diagnoses, the slides were then sent to Dr. Ferenczy, who would provide a diagnosis. If there was complete disagreement, the 4 panel members would discuss the diagnoses and come to a final consensus.

Immunogenicity Endpoints
Consistency Lot substudy

- For immunogenicity, the primary endpoint were GMTs to HPV Types 6, 11, 16, and 18 at Week 4 Postdose 3.

The primary per protocol immunogenicity analyses were assessed in subjects naïve to HPV 6/11, 16 and/or 18.

Safety Endpoints: The important variables of interest were the occurrence of severe injection site adverse events and the incidence of any vaccine related serious adverse event.

S**urveillance/Monitoring:** See Design Overview for procedures.

- Subjects had their oral Temperature (T) taken before each vaccination. Injection was postponed if T $\geq$ 100°F or $\geq$ 37.8°C (oral) within 24 hours prior to an injection.
- A urine pregnancy test was taken prior to each vaccination, and had to be negative in order for the subject to receive the vaccination. If a subject became pregnant during the vaccination period, vaccination was postponed until at least 2 weeks after the resolution of the pregnancy. Subjects who became pregnant after completion of the vaccination series completed study procedures at the discretion of the investigator.
- Breast feeding was not a contraindication to enrollment or vaccination.
- Subjects were monitored for evidence of adverse events for 30 minutes after each vaccination.
- Visible external genital lesions noted during the study period, after Day 1 through Month 48, were to be biopsied.
- Symptomatic subjects may have been seen at an unscheduled visit.

- Subjects in the Non-Serious Adverse Experience (NSAE) substudy were given a Vaccine Report Card (VRC) at each vaccination visit. The subject was to record their oral Temperature 4 hours after the injection and for 4 days thereafter. Any systemic or injection site adverse event was to be recorded for 14 days after each injection. Measurement of solicited injection site AEs (redness, swelling) were to be recorded on the VRC (ruler provided on the VRC).
- Subjects in the United Kingdom were to be queried for non-serious adverse events on their next scheduled visit, but these subjects did not complete a VRC.
- Intensity of adverse events were graded as follows:
  Mild – awareness of sign or symptom
  Moderate – discomfort enough to cause interference with usual activities
  Severe – incapacitating with inability to work or do usual activity
- For the measured adverse experiences of injection-site redness and swelling, 0 to 1 inch was categorized as mild, >1 to $\leq$ 2 inches was categorized as moderate, and >2 inches was categorized as severe.
- Causality was assessed by the investigator.
- The remaining subjects (i.e., those not participating in the NSAE substudy) were solicited only for Serious Adverse Events that occurred in the 14 days after each vaccination. NSAEs could be reported based on investigator discretion.
- For all subjects, SAEs were to be reported from the time the consent was signed through 14 days after the first vaccination, and for 14 days after the other 2 vaccinations, whether or not vaccine related. All deaths, SAEs that led to subject discontinuation, and vaccine related SAEs were to be reported throughout the study. In addition, all pregnancy/labor/delivery related and procedure related SAEs, regardless of causality, were to be reported throughout the study.
- New medical histories were summarized as well and presented in tabular form in each clinical study report.
- Colopscopies were to be performed by an experienced colposcopist according to the protocol specific algorithm. (See **Appendix 3** for colposcopy algorithm, and Efficacy Conclusions for discussion of the algorithms.) (Source: Table 5-4, CSR 015v2, p. 85)

Statistical Considerations

Primary Efficacy Objective (Protocol 015): Administration of 3 doses of Gardasil reduces the incidence of the composite endpoint of HPV 16- and 18-related high-grade cervical abnormalities (CIN 2/3) or HPV 16- and 18-related invasive cervical carcinoma in subjects who are PCR negative and seronegative at baseline and PCR negative 1 month after completion of the vaccination series for the relevant HPV type compared to placebo recipients. The statistical criterion for success for Protocol 015 requires that the lower bound of the confidence interval for the vaccine efficacy excludes 0%. (A combined analysis presented later that includes Protocols 005, 007, 013, and 015 would exclude a lower bound of 25%.)

- Protocol 015 was powered based on a fixed event design with an interim analysis. To ensure adequate power for the interim analysis (80 to 90% power) and the final analysis (90%) for varying true vaccine efficacies after the multiplicity adjustment, at least 19 cases of HPV 16-related or HPV 18-related CIN 2/3 or worse were required for the interim analysis, and 29 cases are required for the final analysis. To observe 29

cases of the primary endpoint by Month 48, an overall sample size of approximately 11,500 subjects (5,750 in each vaccination group) was required for the study.
- Follow-up for the primary efficacy endpoint began following the Month 7 visit.
- The primary outcome of interest in evaluating vaccine efficacy was the combined incidence of HPV 16-related CIN 2/3 or worse and HPV 18-related CIN 2/3 or worse. This endpoint occurred if on any single biopsy, ECC, or LEEP/conization tissue block, the following occurred: Pathology Panel consensus diagnosis of CIN 2, CIN 3 (including squamous carcinoma in situ), adenocarcinoma in situ, invasive squamous cervical carcinoma, or invasive adenocarcinoma of the cervix, **AND** detection of HPV 16 and/or HPV 18 by biopsy Thinsection PCR in an adjacent section from the same tissue block.

Exploratory Efficacy Objectives: There were 2 exploratory efficacy objectives for this study:
- Estimate the impact of the administration of the vaccine on the incidence of the composite endpoint of ALL CIN 2/3 or invasive cervical carcinoma (caused by any vaccine or non-vaccine HPV type) in subjects who are PCR negative and seronegative at baseline and PCR negative 1 month after completion of the vaccination series for high risk HPV types. The first exploratory objective was addressed using the same methodology as for the primary analysis. A normal Pap test result at Day 1 was used as a proxy for assessing baseline negativity for non-vaccine HPV types.
- Estimate the impact of the administration of the vaccine on the incidence of the composite endpoint of HPV 6-, HPV 11-, HPV 16-, and HPV 18-related external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer.
- Other exploratory analyses included incidence of HPV 6, 11, 16, 18 related CIN 1 (or worse), the incidence of external genital lesions irrespective of HPV type, and assessment of potential therapeutic efficacy.

Handling of Individual Missing Data Values
Eligibility for Analysis Population
- Subjects who were missing a baseline serology result for a particular vaccine HPV type could not be assessed for baseline HPV serostatus and were excluded from the PPE, MITT-1, and MITT-2 populations.
- The PCR results for 2 cervicovaginal specimens collected at enrollment and 2 cervicovaginal specimens collected at Month 7 were used to determine each subject's eligibility for analysis. Subjects who were missing one or both of the PCR results for a given vaccine HPV type at enrollment or Month 7 were excluded from the PPE and MITT-1 populations. Subjects missing one or both of the PCR results for a given vaccine HPV type at enrollment were excluded from the MITT-2 population.
- If the PCR result from a biopsy sample taken between enrollment and Month 7 (inclusive) was missing for a given vaccine HPV type, and the biopsy was diagnosed as abnormal, the subject *was not* eligible to be classified as a case of CIN 2/3 or cervical cancer related to that type. If the PCR result was missing and the diagnosis was normal, the subject *was* eligible. (This rule was established because abnormal tissue is likely to be HPV PCR positive.) Subjects who were not eligible to be classified as a case based on a biopsy collected through Month 7 were excluded from

the PPE and MITT-1 populations. Subjects who were not eligible to be classified as a case based on a biopsy collected at enrollment were excluded from the MITT-2 population.

Missing Data During Efficacy Follow-up

- Biopsy, ECC, or LEEP/conization specimens missing PCR result or Pathology Panel diagnosis were not used to classify a subject as a case. Subjects who had a definitive therapy procedure without becoming a case of HPV 16/18-related CIN 2/3 or worse were censored for the primary and secondary efficacy evaluations at the time of the definitive therapy procedure, unless previously classified as a case.
- Results from cervical biopsies and tissue specimens collected outside of the study were not used for the evaluation of HPV 16/18-related CIN 2/3 in the primary efficacy analysis. A sensitivity analysis was performed in which cervical biopsies collected outside of the study were included in the all CIN 2/3 efficacy analysis *only* if a Pathology Panel diagnosis and PCR result were available for the specimen.
- Similar rules were to be applied for the secondary analysis.
- Cases of CIN 2/3 or worse identified at a colposcopy performed due to the presence of an HPV related External Genital lesion Subjects were not included in the primary efficacy analyses, nor were these CIN 2/3 cases counted toward the total number of cases needed to trigger the analyses. Sensitivity analyses were performed in all 4 analysis populations in which all cases of CIN 2/3 or worse were included regardless of the reason for the colposcopy.
- For the exploratory analyses of all other CIN endpoints in the MITT-3 population only, all biopsies were included regardless of reason for colposcopy because the MITT-3 population is intended to closely resemble a “real-world” situation.

Efficacy Analysis Populations: (See Appendix 4)

TABLE 27
Definitions of Efficacy Populations

Efficacy Population	Definition
Per Protocol Efficacy Population	*Received all 3 vaccinations *Sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Did not deviate from protocol *Cases were counted starting 30 days after the 3rd vaccination
MITT-1	*Received all 3 vaccinations *Sero-and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Cases were counted starting 30 days after the 3rd vaccination
MITT-2	*Received at least 1 vaccination *Sero- and PCR negative at Day 1 to appropriate HPV types *Had any follow-up visit after 1 month following the first injection *Cases were counted starting 30 days after the first vaccination
MITT-3	*Received at least 1 vaccination *Included regardless of baseline serology and PCR status *Had any follow-up visit after 1 month following the first injection *Cases were counted starting 30 days after the first injection
Restricted MITT-2	*Seronegative and PCR negative at Day 1 to all vaccine HPV types **and** had a normal Pap test at Day 1 *Cases were counted starting 30 days after the first vaccination

Exploratory Efficacy populations: Therapeutic efficacy was assessed in subjects who were PCR positive and seronegative at baseline, in those who were PCR negative and seropositive at baseline, and in those who were PCR positive and seropositive at baseline.

Consistency Lot Substudy:

- **Primary Immunogenicity Hypothesis** of the Consistency Lot Substudy: Three separate lots of quadrivalent HPV vaccine induce similar immune responses, as measured by the serum cLIA geometric mean titers (GMTs) to HPV 6, 11, 16, and 18, at Week 4 Postdose 3. The statistical criterion for consistency - the upper bound of the confidence interval for the fold difference in GMTs between any 2 lots exclude a fold-difference of 2 or greater for each HPV type.
- **Secondary Immunogenicity Hypothesis** of the Consistency Lot Substudy**:** Three separate lots of quadrivalent HPV vaccine induce similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3. [A fixed cut-off was used in the assays for anti-HPV 6, 11, 16, and 18. The cut-off was derived by repeatedly testing a panel of positive and negative samples against the standard curve. Any sample with a value less than the cut-offs were considered as seronegative. A sample with a value greater than or equal to the cut-off was considered seropositive. Seroconversion was defined as change in serostatus from seronegative to seropositive. The cut-offs for anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.] The statistical criterion for similarity - the upper bound of the confidence interval for the maximum absolute difference in proportions between any 2 of the 3 lots exclude 5 percentage points or more for each HPV type.

Immunogenicity Analysis Populations: The 2 populations of primary interest were the per-protocol immunogenicity (PPI) population and the "all type-specific HPV naïve subjects with serology data" population.

- **Per-Protocol Immunogenicity:** Included subjects in the per-protocol efficacy population who also: (1) received all 3 vaccinations within acceptable day ranges and (2) had postvaccination serum samples collected within the acceptable day ranges.
- **"All Type-Specific HPV Naïve Subjects With Serology Data" Population:** Included all subjects who: (1) received all 3 vaccinations; (2) were seronegative by cLIA to the appropriate HPV vaccine component(s) at enrollment; and (3) were PCR-negative to the appropriate HPV vaccine component(s) from enrollment through Month 7. This population included general protocol violators and considered incorrectly randomized subjects and subjects who received the incorrect clinical material in the analysis according to the treatment group to which they were randomized by the study allocation schedule.

Primary Safety Objective: The sponsor's primary safety objective was to demonstrate that the candidate vaccine was generally well tolerated.
Primary Safety Endpoint: This was the proportion of subjects with vaccine related serious adverse experiences. The proportion of subjects with severe injection-site adverse experiences was also of special interest.

Safety Analysis Population:

- All subjects who received at least 1 injection and had follow-up data were included in the summary of serious adverse experiences.
- All subjects in the detailed NSAE substudy (United States) or in the U.K. who received at least 1 injection and had follow-up data were included in the safety summaries of adverse experiences for the respective cohort.
- Subjects who were incorrectly randomized or who received incorrect clinical material at 1 or more vaccination visits were summarized for safety according to the clinical material they received if they received the same clinical material at all vaccination visits.
- Subjects who received a mixed regimen of clinical material were summarized separately and were not included in formal statistical comparisons.

Interim Analyses and Data Monitoring
Efficacy: The interim analysis of Protocol 015 was performed at the same time as an interim analysis of the **combined data** from Protocols 005, 007, 013, and 015. This was scheduled when at least 19 cases of CIN 2/3 or cervical cancer related to HPV 16 or 18 were observed in Protocol 015 and at least 33 cases were observed in all 4 studies. (At the time of unblinding, 21 cases had accrued in Protocol 015 and 53 cases had accrued in the combined trials.)

- The interim analysis of Protocol 015 was to be performed by a designated unblinded statistician otherwise unrelated to the study. This statistician provided the results of the analysis to a DSMB along with the results of the interim analysis of the combined data (Protocols 005, 007, 013, and 015). The DSMB communicated to the HPV

vaccine project team at the sponsor that the interim analyses of Protocol 015 and the combined data set met the primary statistical criteria for success.

Safety: Safety was monitored during the study by the DSMB, which was to determine whether any actions should be taken based on the data. Approximately every 6 months during the vaccination period and approximately every year thereafter, all available safety data from the study were summarized by vaccination group by the designated unblinded Sponsor statistician and sent to the DSMB. The DSMB in particular monitored the incidence and characteristics of SAEs; the incidence and characteristics of NSAEs; pregnancies and their outcomes; the incidence of breast feeding during the vaccination period and safety outcome in nursing infant; and new medical conditions that arose during the study.

Changes in the Protocol and Changes in Statistical Analyses: Four protocol amendments were submitted to the IND and reviewed prior to unblinding. Several changes were made in the planned statistical analysis prior to unblinding and did not result in major changes to protocol conduct. Several additional changes were made in the planned statistical analyses, necessitated by paucity of cases which precluded performing planned analyses. An exploratory efficacy analysis was conducted in subjects who were initially seropositive and PCR positive for the relevant vaccine HPV type at baseline. See **Appendix 5** for details**.**

<u>Results</u> - Protocol 015

Populations Enrolled/Analyzed

- A total of 12,167 subjects were enrolled. 10 subjects were randomized but not vaccinated. The reasons for these discontinuations included: 1 with an AE, 2 discontinued for other; 5 withdrew consent, and 2 had a protocol deviation.
- 540 subjects were screened but never randomized. The most common reason for non-randomization after screening was the presence of any condition which in the opinion of the investigator interfered with participation (116/540 or 21.5%).
- Overall, 288 subjects (2.4%) discontinued the study during the vaccination period. The most common reasons were withdrawal of consent and lost to follow-up. Compared with the placebo group, slightly more subjects discontinued from the vaccine group as compared to the placebo group.
- Fewer than 1% who entered the follow-up period discontinued study participation.
- Three subjects were prematurely unblinded: AN 4007 (SAE at Month 2), AN 47711 (SAE at Month 6), and AN 55424 (study material information inadvertently released to investigator). All three occurred in Gardasil group.

TABLE 28
Protocol 015: Subject Disposition

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES					539†	
RANDOMIZED	6087		6080		12167	
VACCINATED AT:						
Dose 1	6082	(99.9)	6075	(99.9)	12157	(99.9)
Dose 2	6005	(98.7)	6020	(99.0)	12025	(98.8)
Dose 3	5954	(97.8)	5976	(98.3)	11930	(98.1)
VACCINATION PERIOD (Day 1 Through Month 7)						
ENTERED	6082		6075		12157	
COMPLETED‡	5916	(97.3)	5953	(98.0)	11869	(97.6)
DISCONTINUED	166	(2.7)	122	(2.0)	288	(2.4)
WITH LONG-TERM FOLLOW-UP§	24	(0.4)	14	(0.2)	38	(0.3)
Clinical adverse experience	2	(0.0)	3	(0.0)	5	(0.0)
Other reasons	15	(0.2)	4	(0.1)	19	(0.2)
Pregnancy	7	(0.1)	6	(0.1)	13	(0.1)
WITHOUT LONG-TERM FOLLOW-UP‖	142	(2.3)	108	(1.8)	250	(2.1)
Clinical adverse experience	6	(0.1)	2	(0.0)	8	(0.1)
Lost to follow-up	42	(0.7)	36	(0.6)	78	(0.6)
Moved	13	(0.2)	13	(0.2)	26	(0.2)
Other reasons	9	(0.1)	4	(0.1)	13	(0.1)
Protocol deviations	2	(0.0)	1	(0.0)	3	(0.0)
Withdrew consent	70	(1.2)	52	(0.9)	122	(1.0)
FOLLOW-UP PERIOD (After Month 7)						
ENTERED	5935		5953		11888	
CONTINUING	5895	(99.3)	5919	(99.4)	11814	(99.4)
DISCONTINUED	40	(0.7)	34	(0.6)	74	(0.6)
Clinical adverse experience	2	(0.0)	4	(0.1)	6	(0.1)
Lost to follow-up	18	(0.3)	15	(0.3)	33	(0.3)
Moved	1	(0.0)	4	(0.1)	5	(0.0)
Other reasons	2	(0.0)	3	(0.1)	5	(0.0)
Withdrew consent	17	(0.3)	8	(0.1)	25	(0.2)

† Excludes one non-randomized subject, Baseline Number 4061, for whom age (a criterion required to run this table) was not available.
‡ Subjects completed 3 doses of vaccinations and entered the long-term follow-up period.
§ Subjects received fewer than 3 doses of vaccinations and entered the long-term follow-up period.
‖ Subjects discontinued on or before Month 7 and did not enter the long-term follow-up period.
Status percentages are calculated based on the number of subjects who entered the respective time period.
n = Number of subjects with the indicated characteristic.
AN 57408 discontinued from the vaccination period due to being lost to follow-up. This subject is counted in the With Long-Term Follow-up category but is not included in the individual reason breakout.
HPV = Human papillomavirus; VLP = Virus-like particles; AN = Allocation number.

Source: Table 6-1, CSR 015v2, p. 165

TABLE 29
Protocol 015: Accounting for Substudy Participants

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=6,082)	Placebo (N=6,075)	Total (N=12,157)
HPV 16 Per-Protocol Efficacy Population	4,577	4,430	9,007
Subjects With Post Month 7 Follow-Up	4,552	4,405	8,957
Subjects Without Post Month 7 Follow-Up	25	25	50
HPV 18 Per-Protocol Efficacy Population	5,086	5,004	10,090
Subjects With Post Month 7 Follow-Up	5,051	4,968	10,019
Subjects Without Post Month 7 Follow-Up	35	36	71

N = Number of subjects randomized to the respective vaccination group who received at least one injection.
HPV = Human papillomavirus; PCR = Polymerase chain reaction; VLP = Virus-like particles.

Source: Table 6-2, CSR 015v2, p. 166

The reasons for exclusion of subjects from the PPE population appeared generally balanced between the Gardasil and Placebo groups. The most common reason that the subject was excluded from each of the PPE populations was seropositivity and/or PCR positivity to the relevant HPV type between Day 1 and Month 7.

TABLE 30
Protocol 015: Number of Subjects in Each Efficacy Population

	Gardasil Recipients	Placebo Recipients	Total
Subjects randomized to receive treatment	6087	6080	12167
Subjects who received at least 1 injection	6082	6075	12157
PPE Population for HPV 6/11	4756	4675	9431
Excluded by Month 7 for positivity	(822)	(920)	(1742)
PPE population for HPV 16	4577	4430	9007
Excluded by Month 7 for positivity	(1012)	(1162)	(2174)
PPE population for HPV 18	5086	5004	10090
Excluded by Month 7 for positivity	(443)	(548)	(991)
MITT-1 population (HPV 16/18 CIN 2/3 or worse)	5552	5543	11095
MITT-2 population (HPV 16/18 CIN 2/3 or worse)	5736	5766	11502
RMITT-2 population (CIN due to any type)	3789	3826	7615
MITT-3 population (HPV 16/18 CIN 2/3 or worse)	5947	5973	11920

Source: From Table 6-4, CSR 015v2, p. 169-71 and from Amendment 0021, efficacy information amendment 4/13/06

Demographic Characteristics Protocol 015

The 90 study sites were located in 13 countries in North America, South America, Europe and Asia. The subject characteristics by vaccination group are provided in Table 31 below.

TABLE 31
Protocol 015: Subject Characteristics by Vaccination Group

		Gardasil	Placebo	Total
Characteristic	Parameters or categories	Value or N (%)	Value or N(%)	Value or N (%)
Gender	Female	6087 (100%)	6080 (100%)	12167 (100%)
Age (years)	Mean	20.0	19.9	19.9
	Standard deviation	2.2	2.1	2.1
	Median	20	20	20
	Minimum/Maximum	15-26	15-26	15-26
Race/Ethnicity	Asian	151 (2.5%)	135 (2.2%)	286 (2.4%)
	Black	171 (2.8%)	227 (3.7%)	398 (3.3%)
	Hispanic American	555 (9.1%)	557 (9.2%)	1112 (9.1%)
	Native American	1 (0.0%)	1 (0.0%)	2 (0.0%)
	White	4584 (75.3%)	4550 (74.8%)	9134 (75.1%)
	Other	625 (10.3%)	610 (10.0%)	1235 (10.2%)
Region	North America	460 (7.6%)	456 (7.5%)	916 (7.5%)
	Latin America	1599 (26.3%)	1594 (26.2%)	3193 (26.2%)
	Asia-Pacific	92 (1.5%)	89 (1.5%)	181 (27.4%)
	Europe	3936 (64.7%)	3941 (64.8%)	7877 (64.7%)
Smoking Status	Never smoked	4023 (66.1%)	3959 (65.1%)	7982 (65.6%)
	Ex-smoker	405 (6.7%)	444 (7.3%)	849 (7.0%)
	Current smoker	1658 (27.2%)	1676 (27.6%)	3334 (27.4%)

Source: From Table 6-7, CSR 015v2, p. 177

- The demographic characteristics for the PPE population were similar to those in the overall vaccinated group. (Source: Table 11-4, CSR 015v2, p. 404, not shown here)

Demographic characteristics for each of the 4 geographic regions:

- Differences between the 4 areas with regard to ethnic composition were consistent with the regions' overall demographics. In Europe, there was a higher proportion of subjects who currently smoked (31.2%). The mean age of subject was higher in the Asian group as compared to the population overall (23.1 years). (Source: Tables 11-5, 11-6, 11-7, 11-8, CSR 015v2, p. 405-8, not shown here)
- Within each geographic region, the distribution of age at enrollment into the study was generally comparable between the treatment groups. (Source: Figures 11-1, 11-2, 11-3, 11-4, CSR 015v2, p. 409-12, not shown here).

Summary of Sexual Demographics

- The sexual demographics of the treatment groups were generally comparable.
- The sexual demographics for the PPE population were similar to those in the overall population. (Source: Table 11-9, p. 413, CSR 015v2, not shown here)
- Subjects in Asia-Pacific were older at the time of sexual debut (app. 19 years).
- Subjects in Europe had a higher proportion of subjects with new partners within the last six months (36.8%).

TABLE 32
Protocol 015: Summary of Sexual History at Enrollment by Vaccination Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=6,087)	Placebo (N=6,080)	Total (N=12,167)
	n (%)	n (%)	n (%)
Subjects With Sexual History Data at Enrollment	6,086	6,078	12,164
Virgins	393 (6.5)	410 (6.7)	803 (6.6)
Non-Virgins	5,693 (93.5)	5,668 (93.3)	11,361 (93.4)
Age at First Sexual Intercourse Among Non-Virgins (years)			
Mean	16.6	16.6	16.6
Standard Deviation	1.9	1.9	1.9
Median	17	16	17
Range	5 to 25	4 to 26	4 to 26
Lifetime Number of Male or Female Sexual Partners Among Non-Virgins			
Unknown	0 (0.0)	2 (0.0)	2 (0.0)
1	1,881 (30.9)	1,940 (31.9)	3,821 (31.4)
2	1,386 (22.8)	1,419 (23.3)	2,805 (23.1)
3	1,218 (20.0)	1,155 (19.0)	2,373 (19.5)
4	1,098 (18.0)	1,026 (16.9)	2,124 (17.5)
>4	110 (1.8)	126 (2.1)	236 (1.9)
Median	2	2	2
Number of New Male or Female Sexual Partners in the 6 Months Prior to Study Start Among Non-Virgins			
0	3,860 (63.4)	3,829 (63.0)	7,689 (63.2)
1	1,519 (25.0)	1,525 (25.1)	3,044 (25.0)
2	250 (4.1)	231 (3.8)	481 (4.0)
3	43 (0.7)	55 (0.9)	98 (0.8)
4	10 (0.2)	15 (0.2)	25 (0.2)
>4	11 (0.2)	13 (0.2)	24 (0.2)

Percent is computed as 100*(n/number of subjects with sexual history data at enrollment).
N = Number of subjects randomized.
n = Number of subjects with the indicated characteristic.
HPV = Human papillomavirus; VLP = Virus-like particles.

Source: Table 6-8. CSR 015v2, p. 180

Gynecologic History: The gynecologic history of subjects overall in the Gardasil and placebo groups are shown in Table 32 below.

TABLE 33
Protocol 015: Gynecologic History at Enrollment by Vaccination Group (≥ 1%)

	Gardasil N-6087	Placebo N=6080	Total N=12167
History of Cervical, Vaginal, and Vulvar Surgical Procedures			
Any gynecologic procedure	688 (11.3%)	694 (11.4%)	1382 (11.4%)
C-section	161 (2.6%)	172 (2.8%)	333 (2.7%)
Abortion	48 (0.8%)	71 (1.2%)	119 (1.0%)
Dilitation and extraction	115 (1.9%)	103 (1.7%)	218 (1.8%)
Vaginal or vulvar surgery	398 (6.5%)	386 (6.3%)	784 (6.4%)
History of Genital Tract Infections or Sexually Transmitted Diseases			
Any genital tract infection or STD	1235 (20.3%)	1234 (20.3%)	2469 (20.3%)
Bacterial Vaginosis	233 (3.8%)	261 (4.3%)	494 (4.1%)
Chlamydia trachomatis	380 (6.2%)	344 (5.7%)	724 (6.0%)
Vaginal candidiasis	356 (5.8%)	349 (5.7%)	705 (5.8%)
Other	356 (5.8%)	325 (5.3%)	681 (5.6%)

Source: From Table 6-9, CSR 015v2, p. 182-3

Prevalence of Non-HPV Cervicovaginal Infections at Day 1

- The proportions of subjects with non-HPV cervicovaginal infections at Day 1 in the treatment groups were comparable. (See Table 34 below).
- The baseline prevalence of non-HPV disease was similar in the PPE population (Source: Table 11-19, CSR 015v2, p. 426, not shown here).
- The prevalence of non-HPV cervicovaginal infections was highest in Latin America (9.3%) and lowest in Asia (2.8%)
- Within a region, the prevalences were generally comparable between the two groups. (Source: Tables 11-20, 11-21, 11-22, 11-23, CSR 015v2, p. 427-30, not shown here)

TABLE 34
Protocol 015: Prevalence of Non-HPV CV Infections and STDs at Day 1 by Vaccination Group

	Gardasil N=6087	Placebo N=6080	Total N=12167
Overall Baseline Prevalence			
Any Non-HPV CV infections of STD	309 (5.1%)	265 (4.4%)	574 (4.7%)
Mandatory Tests			
Chlamydia	258 (4.3%)	225 (3.8%)	483 (4.0%)
Gonorrhea	25 (0.7%)	13 (0.3%)	38 (0.5%)

Source: From Table 6-10, CSR 015v2, p. 185

Pregnancy History at Day 1

- Overall, approximately 80% of subjects reported no prior pregnancies. The proportions were comparable between the vaccine and placebo groups. These proportions were similar in the PPE population. (Source: Table 6-11, p. 187-8 and Table 11-24, p. 431-2, CSR 015v2, not shown here)

Contraceptive Use Prior to Day 1

- Overall, approximately 50% of subjects used hormonal contraceptives, and 26% used male condoms for both treatment groups, and the proportions were generally comparable between the vaccine and placebo groups. (Source: Table 6-12, p. 189-90 and Table 11-29, p. 440-1, CSR 015v2, not shown here)

HPV Related Pathology at Day 1

- The proportions of subjects with an abnormal Pap test at Day 1 were similar in the two treatment groups. (See Table 35 below).
- The proportions of subjects with HPV related pathology at Day 1 were similar in the PPE population. (Source: Table 11-34, CSR 015v2, p. 449, not shown here)
- For the 4 geographic regions, the proportion of subjects in the Asia-Pacific area with SIL was lowest (3.9%) as compared to the other areas, where the proportions are similar to those seen in the overall population. (Source: Tables 11-35, 11-36, 11-37, 11-38, CSR 015v2, p. 450-3, not shown here)

TABLE 35

Protocol 015: Summary of Pap Test Results at Day 1 by Vaccination Group

	Gardasil N=6087	Placebo N=6080	Total N=12167
Number with Day 1 Pap test result	6025	6008	12033
Day 1 Pap test satisfactory	5919 (98.2%)	5896 (98.1%)	11815 (98.2%)
SIL Present	697 (11.8%)	654 (11.1%)	1351 (11.4%)
ASC-US	280 (4.7%)	274 (4.6%)	554 (4.7%)
ASC-H	21 (0.4%)	18 (0.3%)	39 (0.3%)
LSIL	352 (5.9%)	326 (5.5%)	678 (5.7%)
HSIL	42 (0.7%)	33 (0.6%)	75 (0.6%)
Atypical glandular cells	2 (0.0%)	3 (0.1%)	5 (0.0%)

Source: From Table 6-13, CSR 015v2, p. 192

HPV 6, 11, 16, 18 Serostatus and DNA Detection at Day 1

- Overall, in both treatment groups, 19.9% of subjects were positive by serostatus, and 15.5% were positive by PCR.
- **Overall, 27.3% of subjects were positive by serology or PCR.** (Source: Table 6-14, CSR 015v2, p. 193, not shown here)
- Regionally, overall positivity was highest in Latin America (32.3% by either method) and lowest in Asia (14.9% by either method). (Source: Tables 11-39, 11-40, 11-41, 11-42, CSR 015v2, p. 454-7, not shown here)
- The proportions of subjects found to be anti-HPV 6, 11, 16, and 18 seropositive were generally comparable between the 2 treatment groups.
- For subjects anti-HPV cLIA results available at Day 1, 11.1% of subjects overall were anti-HPV 16 seropositive; 8.5% of subjects overall were anti-HPV 6 seropositive; 3.8% were anti-HPV 18 seropositive, and 2% were anti-HPV 11 seropositive. (Source: Table 6-15, CSR 015v2, p. 195-196, not shown here)

HPV 6, 11, 16, 18 DNA Detection at Day 1

- Overall, 15.5% of subjects were HPV DNA positive for at least one of the four vaccine types. The proportions with HPV DNA for vaccine HPV types were generally comparable between the vaccine and placebo groups.
- HPV 16 DNA was the most prevalent type (9.1% overall), HPV 6 DNA was next most prevalent (4.3% overall), HPV 18 DNA was next most prevalent (3.9% overall), and HPV 11 DNA least prevalent (0.7%). (Source: Table 6-16, CSR 015v2, p. 198, not shown here)
- Most subjects who had presence of vaccine HPV DNA were positive to one type only.
- **Multiple vaccine HPV types:** Overall, 2.2% of subjects overall had two vaccine HPV types detected (most commonly HPV 16 and 6), and 0.2% had 3 vaccine HPV types detected. (Source: Table 6-17, CSR 015v2, p. 200, not shown here)

Prior Medications and Prior Vaccines (3 days prior to vaccination 1)

- Among all vaccinated subjects, the most common therapies taken were hormonal contraceptives and vitamins.
- The proportions of subjects using these products were generally comparable between treatment groups. (Source: Table 6-18, p. 203, and Table 11-55, p. 478-92, CSR 015v2, not shown here)

Concomitant medications

- In the 916 subjects in the NSAE substudy in the US, app. 92% of subjects received concomitant medications.
- The most common category of medications taken was hormonal contraceptives, followed by medications with anti-inflammatory and analgesic properties. (Source: Table 6-19, CSR 015v2, p. 205-8, not shown here)

Prior Medical History

- The most commonly reported illnesses were dysmenorrhea, seasonal allergy, episiotomy, and gynecological Chlamydia infection.
- Past medical histories were generally comparable in the two vaccination groups. (Source: Table 6-21, CSR 015v2, p. 210- 2, not shown here)

Treatment Compliance

- Approximately 2% of subjects in both vaccination groups received the second dose of study material more than 3 weeks from the scheduled time of the Month 2 vaccination, and approximately 12% of subjects in both groups received study material 4 or more weeks earlier than scheduled for the third dose. The numbers of subjects were comparable in the vaccine and placebo groups. (Source: Figures 6-2 and 6-3, CSR 015v2, p. 213-4, not shown here)

Completion of Scheduled Visits during efficacy follow-up period

- 93.9% of the vaccine group and 94.7% of the placebo group completed the Month 24 visit. Very few subjects in the study report had a Month 36 visit because the fixed event analysis occurred before that time. (Source: Table 6-22, CSR 015v2, p. 215, not shown here)

- The intervals between Months 7-12 and Months 12-24 were very similar in the vaccine and placebo groups. (Source: Table 6-23, CSR 015v2, p. 216, not shown here)

Efficacy Endpoints/Outcomes

Primary Efficacy Hypothesis: The interim analysis occurred on 8/12/05, and the clinical, regulatory, statistical, and data management personnel were unblinded to allow preparation of this CSR. Protocol 015 is expected to continue until 29 cases in the PPE have accrued. This continuation is to be considered an extension study. See "Post-Marketing Commitments" for further information.

- For the analysis of a given endpoint in each of the analysis populations, only subjects who had at least one follow-up visit or the given endpoint contributed.
- The last date of follow-up for cervical endpoints was the date representing the last opportunity to observe a cervical endpoint, defined as the latest of the subject's cervical specimens (biopsies, ECCs, definitive therapies and Pap tests).
- The last date of follow-up for external genital lesion endpoints was the date representing the last opportunity to observe an external genital endpoint, defined as the later of the last scheduled visit and the last unscheduled visit at which an external genital exam or biopsy was performed.
- Therefore, a different number of subjects might contribute to the cervical endpoints as compared to the external genital endpoints. In the per-protocol and MITT-1 analyses, more subjects had post Month 7 follow-up for the external genital endpoints than for the cervical endpoints. The main reason for this difference was that subjects who had cervical definitive therapy were censored at the time of their definitive therapy (i.e., they were ineligible to contribute follow-up time for the analysis of the cervical endpoints after definitive therapy.) These subjects could contribute to evaluation of external genital endpoints.
- In the MITT-2 and MITT-3 analyses, more subjects had follow-up starting 30 days after Day 1 for the external genital endpoints than for cervical endpoints. Pap testing was required to be performed at Day 1 and Month 7 and subsequently every year, although external genital lesions could be followed at each visit. It was possible for a subject who discontinued the study during the vaccination phase to have a Pap test at Day 1 and have a follow-up for external genital lesions in the vaccination phase.

Counting Individual Endpoints within Composite endpoints

- Many of the efficacy endpoints are composite endpoints, including more than one lesion type and/or more than one HPV type. For example, if a subject met the criteria for one or more of the components of a composite endpoint, she was counted as a case for the composite endpoint once. However, she was also counted as a case in each of the component caused lesions. For example, a subject may have developed CIN 2 with HPV 18 at Month 20, and CIN 3 at Month 24 with HPV 16. She was counted as a single case of HPV 16/18 related CIN 2/3 or worse, but could also be counted as a case if HPV 16 related CIN 2/3 and HPV 18 related CIN 2/3. (**See Appendix 6 for details)**

Reviewer's Comment on Exploratory Analyses below: Many of the exploratory analyses are presented separately for Study 015 (and Study 013 as well). These

exploratory analyses are presented for the combined studies in the overview of efficacy as well.

Primary Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse
Efficacy Against HPV 16/18 related CIN 2/3 in PPE population

- The primary analysis of efficacy was conducted in the PPE population (**see Appendix 4).**
- **In the PPE population,** for the **specific vaccine HPV type for which the subject was naïve (seronegative at baseline and PCR negative at baseline through Month 7)**, there was a high degree of efficacy against lesions related to that specific HPV type. However, a subject who was a member of the PPE population for HPV 16 might not be a member of the other PPE populations (e.g., for HPV 18 and/or HPV 6). That subject might still have developed a lesion related to a pre-existing vaccine HPV type (e.g., CIN 2/3 due to pre-existing HPV 18 or 6). The subject would be excluded from the PPE populations for HPV 18 and HPV 6, but be included in the PPE population for HPV 16.

TABLE 36
Protocol 015: Primary Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse by HPV type and Severity (PPE Population)

	Gardasil N=6082				**Placebo** N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN 2/3 or Worse	5301	0	7435.1	0	5258	21	7385.5	0.3	**100%**	75.8, 100%
By HPV Type										
HPV 16 Related CIN 2/3 or Worse	4552	0	6407.9	0	4405	16	6215.7	0.3	**100%**	74.8, 100%
HPV 18 Related CIN 2/3 or Worse	5051	0	7083.2	0	4968	8	6980.2	0.1	**100%**	42.3, 100%
By Lesion Type										
CIN 2	5301	0	7435.1	0	5258	15	7386.3	0.2	**100%**	72.3, 100%
CIN 3	5301	0	7435.1	0	5258	15	7386.3	0.2	**100%**	72.0, 100%
AIS	5301	0	7435.1	0	5258	1	7387.3	0.01%	**100%**	<0.0, 100%
Cervical Cancer	5301	0	7435.1	0	5258	0	7387.4	0.0	**N/A**	N/A

Source: Table 7-2, CSR 015v2, p. 229, Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2

- The required number of cases (19) was reached after an average of 1.4 years of follow-up after the Month 7 visit. Most of the cases occurred between 1.4 – 2 years after Month 7.
- Subjects who developed a case of incident HPV 16 or HPV 18 related CIN 2/3 or AIS were more sexually active and more likely to have non-HPV related STDs than the general study population.
- **Treatment by region interaction:** In the placebo population, the incidence of HPV 16/18 related CIN 2/3 or worse was highest in North America (0.8 per 100 person years at risk) and lowest in Asia (0.0 per 100 person years at risk) and Latin America (0.3 per 100 person years at risk). No cases were observed in Asia. There were a limited number of subjects in this region.

Efficacy Against HPV 16/18 related CIN 2/3 or worse in MITT-1, MITT-2 populations

- These populations are similar to the PPE population in that analysis is conducted for the vaccine HPV type to which the subject is naïve (seronegative and PCR negative at baseline).
- The **MITT-1 population** includes protocol violators but is otherwise the same as the PPE population. In this population, there are 2 additional cases in the placebo group: one subject received a non-study vaccine within 14 days of vaccination, and one subject received the 3 injections in over 1 year. (Source: Table 7-3, CSR 015v2, p. 234, not shown here)
- The **MITT-2 population** includes protocol violators and cases are counted starting 30 days after the first vaccination. The additional 14 cases in this population included 13 in the placebo group and 1 in the vaccine group. These subjects became PCR positive and/or seropositive for the relevant HPV type by Month 7 (in the vaccine recipient, the case was a CIN 2 associated with HPV 16). (See Table 37 below.)

TABLE 37
Protocol 015: Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse by HPV Type and Severity (MITT-2 Population)

	Gardasil' N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN 2/3 or Worse	5736	1	10797.2	0	5766	36	10881.5	0.3	**97.2%**	83.4, 99.9%
By HPV Type										
HPV 16 Related CIN 2/3 or Worse	4944	1	9350.3	0	4957	28	9392.6	0.3	**96.4%**	78.3, 99.9%
HPV 18 Related CIN 2/3 or Worse	5477	0	10313.6	0	5508	11	10408	0.1	**100%**	59.8, 100%
By Lesion Type										
CIN 2	5736	1	10797.2	0	5766	27	10883.1	0.2	**96.3%**	77.4, 99.9%
CIN 3	5736	0	10797.2	0	5766	24	10885.5	0.2	**100%**	83, 100%
AIS	5736	0	10797.2	0	5766	4	10886.8	0.04	**100%**	<0.0, 100%
Cervical Cancer	5736	0	10797.2	0	5766	0	10887.1	0.0	**N/A**	N/A

Source: Table 7-4, CSR 015v2, p. 235 and Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2

Efficacy Against HPV 16/18 related CIN 2/3 or worse in MITT-3 Population

- The **MITT-3 population** is one in which all subjects are assessed for vaccine efficacy, regardless of baseline HPV status starting 30 days after dose 1. Additional cases of HPV 16/18 related CIN 2/3 in this population occurred among subjects who were already PCR positive and/or seropositive for either HPV 16 or 18 at Day 1 in both the Gardasil and placebo groups. The point estimate for efficacy is lower in this group (39.2%, 95% CI: 16.9, 55.8%) as compared to the PPE population.

Reviewer's Comment: When one compares the number of cases added to each treatment group by adding cases regardless of baseline sero- and/or PCR status to relevant vaccine HPV type, there are slightly more cases of HPV 16 and/or 18 CIN 2/3 added to the placebo group (+75) as compared to the Gardasil group (+66). (See Table 38 below).

TABLE 38
Protocol 015: Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse by HPV Type and Severity (MITT-3)

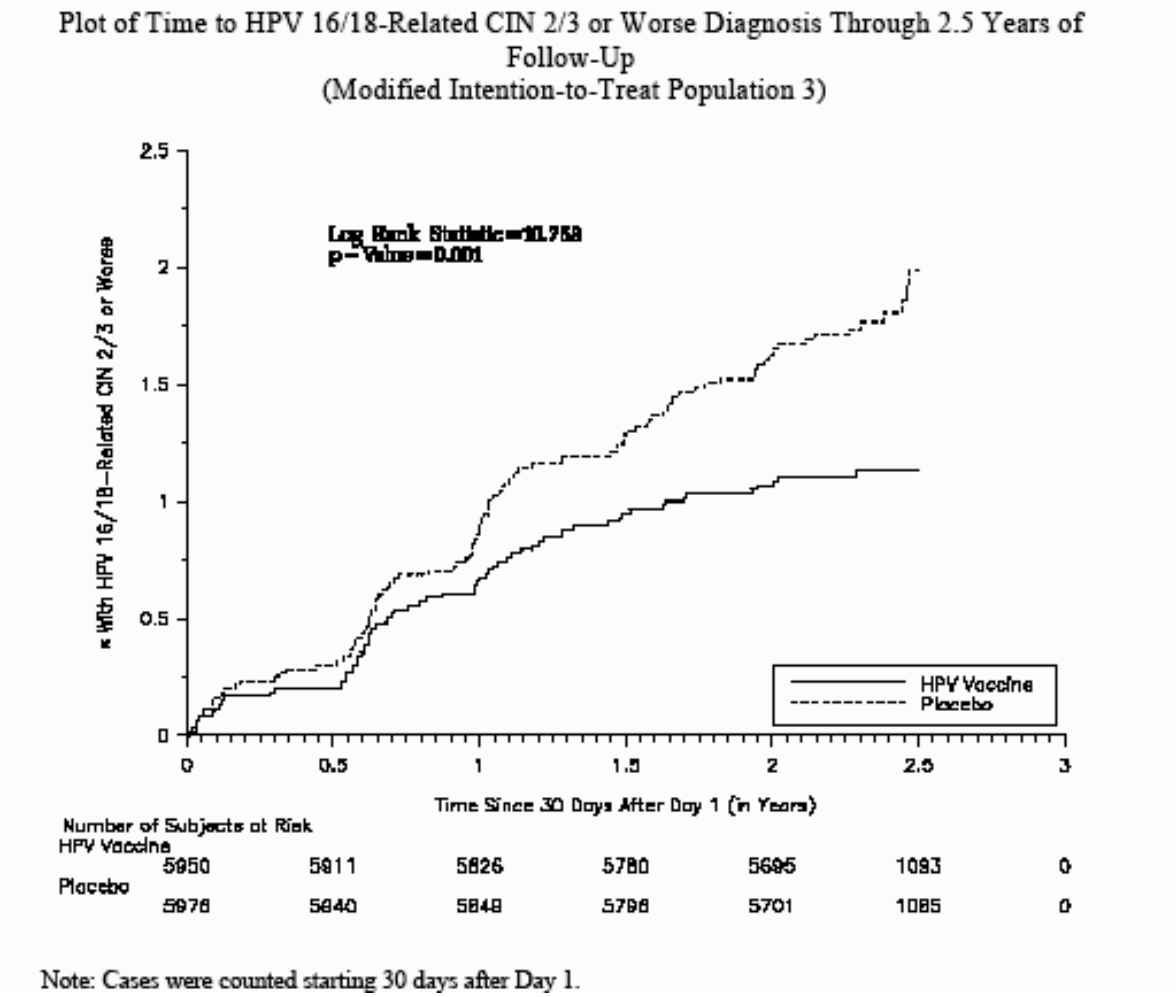
	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN 2/3 or Worse	5947	67 (+66)*	11159.5	0.6	5973	111 (+75)*	11243.9	1.0	**39.2%**	16.9, 55.8%
By HPV Type										
HPV 16 Related CIN 2/3 or Worse	5947	62	11161.1	0.6	5973	99	11247.4	0.9	**36.9%**	12.4, 54.8%
HPV 18 Related CIN 2/3 or Worse	5947	5	11175.5	0	5973	22	11264.1	0.2	**77.1%**	38, 93.2%
By Lesion Type										
CIN 2	5947	36	11169.5	0.3	5973	74	11254.8	0.7	**51%**	26, 68%
CIN 3	5947	45	11168.4	0.4	5973	80	11256.9	0.7	**43.3%**	17.3, 61.6%
AIS	5947	4	11176.9	0.04	5973	6	11267.5	0.1	**32.8%**	<0.0, 86.1%
Cervical Cancer	5947	0	11178.0	0.0	5973	0	11267.9	0	**N/A**	N/A

*Number of cases of HPV 16/18 CIN 2/3 added to each treatment group when subjects are included in the analysis regardless of baseline sero and/or PCR status.
Source: Table 7-5, CSR 015v2, p. 236 Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2

- Figure 6 below shows a plot of time to HPV 16/18 Related CIN 2/3 or worse through 2.5 years of follow-up in the MITT-3 population.

Reviewer's Comment: There is a suggestion of a lower risk of developing CIN 2 or worse related to HPV 16 and/or 18 in Gardasil recipients as time progresses. However, not all subjects have been followed to the later time points, and further follow-up is necessary before a definitive conclusion is reached.

FIGURE 6
Protocol 015



Note: Cases were counted starting 30 days after Day 1.
Source: Figure 11-5, CSR 015v2, p. 651

Sensitivity Analyses

- There were no significant changes in vaccine efficacy when cases of HPV 16/18 related CIN 2/3 were identified due to colposcopy performed for an external genital lesion; when imputing or not imputing cases of missing data (Source: Table 11-81, CSR 015v2, p. 652, not shown here); when including biopsies performed outside the study [Source: Table 11-82, CSR 015v2, p. 653, not shown here]; or when the histopathological diagnosis was from the central lab as compared to the Pathology Panel (Source: Tables 7-7 and 7-8, CSR 015v2, p. 241-2, not shown here).

Exploratory Analysis of Vaccine Efficacy against the combined incidence of HPV 6, 11, 16, or 18 related CIN

Efficacy Against HPV 6, 11, 16 or 18 related CIN in PPE Population

- The VE with respect to the combined incidence of HPV 6, 11, 16 , or 18 related CIN was 91% (95% CI: 74%, 98%) in the PPE population.
- There were 4 cases of HPV 16 related CIN 1 in the vaccine group and 25 in the placebo group. These 4 cases in vaccine recipients are presented:
  - **AN 40887:** A W Finnish woman who developed a case of HPV 16 related CIN 1 at Month 13. At Day 1, she was 17 years old, reported 4 lifetime partners, was negative for Chlamydia and negative for all vaccine types by serology and PCR. She was also PCR negative at Month 7. Her Pap was negative at Day 1, but she developed LSIL at Month 7 and again at Month 12, leading to colposcopy and HPV 16 related CIN 1. She did not participate in the Consistency Lot substudy, so Month 7 levels of anti-HPV antibodies are not available.
  - **AN 54999:** A W British woman who developed HPV 16 related CIN 1 at Month 13. At Day 1, she was 22 years of age and reported 2 lifetime partners. There was no evidence of other STDs. At Day 1 and Month 7, she was seropositive and PCR positive for HPV 18. She was seronegative for the other vaccine HPV types at Day 1, and PCR negative for the other vaccine HPV types from Day 1 through Month 7. She had detectable antibody to HPV 16 at Day 1 (18 mMU/mL) although this level did not meet the criteria for seropositivity. There was a Pap dx of LSIL at Day 1 and HSIL at Month 7, which led to a colposcopy at Month 9, resulting in a dx of HPV 18 related CIN 3. She underwent definitive therapy at Month 13. One biopsy specimen tested positive for HPV 16 and HPV 18 DNA and was read as CIN 1 by the pathology panel. This subject had a good antibody response, especially to HPV 16 and 18.
  - **AN 55940**: Hispanic Mexican woman who developed a case of HPV 16 related CIN 1 at Month 13. At Day 1, she was 23 years old, and gave a history of 3 lifetime partners. Chlamydia test was positive, and she was negative for all vaccine HPV types by serology and PCR. She was also PCR negative at Month 7, but developed LSIL at that time, and again at Month 12. This led to a colposcopy with the finding of CIN 1 related to HPV 16. Her Month 7 anti-HPV 16 level was very high.
  - **AN 56244**: Hispanic Mexican woman who developed a case of HPV 16 related CIN 1 at Month 12. At day 1, she was 20 years of age, reported 2 sexual partners, was Chlamydia negative, and negative for a new sexual partner during the course of the study. She was positive for multiple cervicovaginal infections between Day 1 and Month 12. Her anti-HPV 16 antibody level was lower than the PPI population and consistency lot substudy of Protocol 015.

Reviewer's Comment: One subject likely had prior infection with HPV 16. Two subjects developed LSIL by Month 7, and one of these subjects had a very high anti-HPV 16 level, so she may have had prior infection. The other subject had a lower than usual anti-HPV 16 level, but the significance of this finding is not clear.

TABLE 39
Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN by HPV Type and Severity (PPE Population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV6/11/16/18 Related CIN	5383	4	7542.1	0.1	5370	43	7534	0.6	**90.7%**	74.4, 97.6%
BY HPV Type										
HPV 6 related CIN	4723	0	6622.1	0	4643	11	6514.2	0.2	**100%**	60.8, 100%
HPV 11 related CIN	4723	0	6622.1	0	4643	2	6515.4	0	**100%**	<0, 100%
HPV 16/18 related CIN	5301	4	7431.5	0.1	5258	33	7381.7	0.4	**88%**	66.1, 96.9%
HPV 16 related CIN	4552	4	6404.2	0.1	4405	25	6212.5	0.4	**84.5%**	55.1, 96.1%
HPV 18 related CIN	5051	0	7083.2	0	4968	11	6979.5	0.2	**100%**	60.7, 100%
By Lesion Type										
CIN 1	5383	4	7542.1	0.1	5370	31	7535.7	0.4	**87.1%**	63.5,n 96.7%
CIN 2/3 or worse	5383	0	7545.7	0	5370	22	7541.5	0.3	**100%**	81.8, 100%
CIN 2	5383	0	7545.7	0	5370	16	7542.3	0.2	**100%**	74.1, 100%
CIN 3	5383	0	7545.7	0	5370	15	7542.8	0.2	**100%**	72.1, 100%
AIS	5383	0	7545.7	0	5379	1	7543.5	0.01	**100%**	<0.0, 100%
Cervical Cancer	5383	0	7545.7	0	5370	0	7543.6	0	**NA**	N/A

Source: Table 7-9, CSR 015v2, p. 246 Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2

Efficacy Against HPV 6, 11, 16, or 18 related CIN in MITT-1 and MITT-2 Populations

- The vaccine efficacies in each of these populations (MITT-1 [91.3%: 95% CI 76.1, 97.7%] and MITT-2 [91.1%: 95% CI 80.7, 96.5%]) are similar to that seen in the PPE population (because the analysis focuses on those naïve for a specific vaccine HPV type separate from other vaccine types.) (Source: Tables 11-84 and 11-85, CSR 015v2, p. 655-6, not shown here)
- Of the 36 cases who developed a case of vaccine HPV related CIN in the MITT-2 analysis compared to the MITT-1 population, 3 were vaccine recipients and 33 were placebo recipients. All but one of the cases was PCR positive at Month 7 to the HPV type that classified it as a case. One placebo recipient who became a case had PCR data missing at Month 7. (Source: Table 11-87, CSR 015v2, p. 658, not shown here)

Efficacy Against HPV 6, 11, 16, or 18 related CIN in MITT-3 Population

- This is shown in Table 39 below. The VE was lower in this population (46.6%, 95% CI: 31.8, 58.4%) as compared to the PPE population.
- This population includes all subjects regardless of baseline HPV status (i.e, naïve [seronegative and PCR negative] and non-naïve [seropositive and/or PCR positive] subjects). As noted earlier in the analysis of population characteristics, 27% of subjects overall were non-naïve to at least one vaccine HPV type.

Reviewer's Comment: When one compares the number of cases added to each treatment group by adding cases regardless of baseline sero- and/or PCR status to relevant vaccine HPV type, there are slightly more cases of HPV 6/11/16/18 related CIN added to the placebo group (+113) as compared to the Gardasil group (+95). (See Table 40 below).

TABLE 40
Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN by HPV Type and Severity (MITT-3 Population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV6/11/16/18 Related CIN	5947	102 (+95)*	11129.9	0.9	5973	192 (+113)*	11186.3	1.7	**46.6%**	31.8, 58.4%
By HPV Type										
HPV 6 related CIN	5947	8	11171.9	0.1	5973	25	11257.6	0.2	**67.8%**	26.3, 87.4%
HPV 11 related CIN	5947	4	11176.6	0.04	5973	7	11262.5	0.1	**42.4%**	<0.0, 87.6%
HPV 16/18 related CIN	5947	93	11137.4	0.8	5973	174	11197.8	1.6	**46.3%**	30.5, 58.7%
HPV 16 related CIN	5947	86	11141.7	0.8	5973	149	11212.6	1.3	**41.9%**	23.8, 56.0%
HPV 18 related CIN	5947	10	11173.7	0.1	5973	39	11252.7	0.3	**74.2%**	47.3, 88.5%
By Lesion Type										
CIN 1	5947	55	11145.1	0.5	5973	125	11206.1	1.1	**55.8%**	38.8, 68.4%
CIN 2/3 or worse	5947	68	11159.1	0.6	5973	116	11242.9	1.0	**40.9%**	19.7, 56.9%
CIN 2	5947	37	11169.5	0.3	5973	77	11254.6	0.7	**51.6%**	27.4, 68.2%
CIN 3	5947	45	11168.4	0.4	5973	83	11256.1	0.7	**45.4%**	20.5, 62.9%
AIS	5947	4	11176.9	0.04	5973	6	11267.5	0.05	**32.8%**	<0.0, 86.1%
Cervical Cancer	5947	0	11178.0	0.0	5973	0	11267.9	0.0	**NA**	NA

*Number of cases of HPV 6/11/16/18 CIN added to each treatment group when subjects are included in the analysis regardless of baseline sero and/or PCR status. Source: Table 11-86, CSR 015v2, p. 657 and Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2

Efficacy Against HPV 6, 11, 16, or 18 related CIN with 1 or 2 vaccinations

- Of 48 subjects who received one or two vaccinations, there were no cases of HPV 6/11/16/18 related CIN in either Gardasil or placebo recipients. (Source: Table 11-88, CSR 015v2, p. 659, not shown here)

Sensitivity Analyses

- There were no significant changes in vaccine efficacy when cases of HPV 6/11/16/18 CIN when including biopsies performed outside the study (Source: Table 11-91, CSR 15v2, p. 662, not shown here); or when the histopathological diagnosis was from the central lab as compared to the Pathology Panel (Source: Tables 11-89, 11-90, 11-92 CSR 015v2, p. 660-1, p. 663-4, not shown here).

Exploratory Analysis of Vaccine Efficacy Against Combined Incidence of HPV 6, 11, 16, or 18 related External Genital Lesions (EGLs)

Efficacy Against HPV 6, 11, 16, or 18 related EGLs in PPE Population:

- The VE with respect to the combined incidence of HPV 6, 11, 16 , or 18 related EGLs was 98.6% (95% CI: 91.8, 100%) in the PPE population. (See Table 41 below.)

TABLE 41
Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 Related EGL by HPV type and Lesion Type (PPE Population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 related EGL	5401	1	7545.8	0	5387	70	7513.7	0.9	**98.6%**	91.8, 100%
By HPV Type										
HPV 6 related EGL	4738	1	6617.7	0	4656	56	6495.0	0.9	**98.2%**	89.8, 100%
HPV 11 related EGL	4738	0	6619.0	0	4656	9	6512.8	0.1	**100%**	50.1, 100%
HPV 16 related EGL	4558	0	6374.5	0	4410	15	6161.4	0.2	**100%**	73.1, 100%
HPV 18 related EGL	5067	0	7073.7	0	4980	6	6965.3	0.1	**100%**	16.4, 100%
By Lesion Type										
Condyloma, VIN 1, VaIN 1	5401	1	7545.8	0	5387	65	7514.6	0.9	**98.5%**	91.2, 100%
VIN 2/3 or VaIN 2/3	5401	0	7547.1	0	5387	6	7535.4	0.1	**100%**	15.2, 100%
Vulvar or Vaginal Cancer	5401	0	7547.1	0	5387	0	7536.7	0	**NA**	NA

Source: Table 7-10, CSR 015v2, p. 249

- One subject (AN 57819) in the vaccine group developed an HPV 6 related vulvar genital wart 3 months postdose 3 (in the PPE). This subject was a Caucasian American who enrolled in the study at age 18 years. At Day 1, she reported a history of 2 lifetime partners, was negative for Chlamydia and negative for all vaccine HPV types, and had a negative Pap. She remained negative for vaccine HPV types at Month 7. At Month 7, her anti-HPV 6 antibody level was 385 mMU/mL (the Month 7 level in the Per Protocol Immunogencity population was 527.6 mMU/mL). Her Month 7 Pap was normal and her gyn exam was negative. Two months later, she was diagnosed with condyloma accuminata (biopsy confirmed, HPV 6 positive lesion). Another biopsy at Month 12 was also positive for condyloma accuminata, and was again HPV 6 positive.

Efficacy Against HPV 6, 11, 16, or 18 related EGLs in MITT-1 and MITT-2 Populations

- There were no additional cases in the MITT-1 analysis.
- The VE against vaccine type HPV related EGLs was similar in the MITT-2 population as compared to the PPE population (overall VE = 94.6%: 95% CI = 87.8, 98.1%). There were 5 additional cases in the vaccine group in the MITT-2 population analysis, and most were low grade and related to HPV 6. There was also one HPV 16 related EGL. There were no cases of VIN 2/3 or VaIN 2/3 in this population in the Gardasil group, and 16 in the placebo group. (Source: Table 11-93, CSR 015v2, p. 665, not shown here)

Efficacy Against HPV 6, 11, 16, or 18 related EGLs in MITT-3 Population:
The VE against HPV 6, 11, 16, or 18 related EGLs in this population is lower (71.0%, 95% CI: 58.8, 79.9%) as compared to the PPE population. However, the VE in this population against vaccine HPV type related EGLs was higher as compared to the VE in this population against HPV type related CIN.
Reveiwer's Comment: This may be related to a lower prevalence of external genital disease present at baseline (i.e., they are more easily diagnosed in subjects and therefore subjects with EGLs would be excluded prior to participation in the study.) This may also be related to a shorter time to development of at least some of these lesions, e.g., condylomata. When one compares the number of cases added to each treatment group by adding cases regardless of baseline sero- and/or PCR status to relevant vaccine HPV type, there were a slightly higher number of cases of HPV 6/11/16/18 related EGL added to the Gardasil group (+36) as compared to the placebo group (+34). (See Table 42 below).

TABLE 42
Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 Related EGL by HPV Type and Lesion Type (MITT-3 Population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 related EGL	6016	42 (+36)*	11165.8	0.4	6027	145 (+34)*	11183.8	1.3	**71.0%**	58.8, 79.9%
By HPV Type										
HPV 6 related EGL	6016	36	11175.2	0.3	6027	114	11204.3	1.0	**68.3%**	53.6, 78.9%
HPV 11 related EGL	6016	2	11214.0	0.02	6027	18	11273.7	0.2	**88.8%**	53.3, 98.7%
HPV 16 related EGL	6016	6	11208.5	0.1	6027	34	11266.4	0.3	**82.3%**	57.3, 93.9%
HPV 18 related EGL	6016	1	11216.0	0.01	6027	12	11278.5	0.1	**91.6%**	43.4, 99.8%
By Lesion Type										
Condyloma, VIN 1, VaIN 1	6016	40	11168.8	0.4	6027	132	11190.7	1.2	**69.6%**	56.5, 79.2%
VIN 2/3 or VaIN 2/3	6016	4	11213.8	0.04	6027	18	11276.3	0.2	**77.7%**	32.2, 94.5%
Vulvar or Vaginal Cancer	6016	0	11217.4	0.0	6027	0	11286.4	0.0	**NA**	NA

*Number of cases of HPV 6/11/16/18 EGL added to each treatment group when subjects are included in the analysis regardless of baseline sero and/or PCR status.
Source: Table 11-94, CSR 015v2, p. 666

Exploratory Analyses of Vaccine Efficacy Against All CIN

Efficacy Against Any HPV related CIN in the RMITT-2 Population

- These analyses are shown in Table 43 below. This population includes subjects who are naïve to all 4 vaccine HPV types and had a normal Pap test at baseline. Since PCR testing was not completed for non-vaccine HPV types prior to submission of the BLA, this population was to approximate a population naïve to all 4 vaccine types as well as to non-vaccine HPV types (because of the negative Pap test). However, a single Pap test is not 100% sensitive for detecting dysplastic lesions, so it is possible that some of these subjects were previously exposed to a non-vaccine HPV type. The point estimate of efficacy against any CIN was relatively low (19.8%) and did not reach statistical significance (95% CI: < 0, 38.0%). However, the point estimate for efficacy against CIN 2/3 or worse is somewhat higher (36.5%), although this does not reach statistical significance (95% CI: <0, 60.5%).

TABLE 43
Protocol 015: Analysis of Efficacy Against CIN Irrespective of HPV Type (Restricted MITT-2 population)*

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
CIN Due to any HPV type	3789	112	7140.5	1.6	3826	141	7212.2	2	19.8%	<0, 38%
CIN 1	3789	99	7148.5	1.4	3826	122	7221.1	1.7	18.0%	<0, 37.8%
CIN 2/3 or worse	3789	32	7186.6	0.4	3826	51	7272.7	0.7	36.5%	<0. 60.5%
CIN 2	3789	22	7189.9	0.3	3826	41	7276.2	0.6	45.7%	6.7, 69.2%
CIN 3	3789	18	7192.3	0.3	3826	29	7280.1	0.4	37.2%	< 0, 67.1%
AIS	3789	0	7195.8	0.0	3826	2	7283.3	0.03	100%	<0.0, 100%
Cervical cancer	3789	0	7195.8	0	3826	0	7283.6	0	NA	NA

*Restricted MITT-2 population: Subjects were seronegative and PCR negative to all 4 vaccine HPV types and had a negative Pap test at Day 1. Cases were counted starting 30 days after dose 1.
Source: Table 7-12, CSR 015v2, p. 256 and Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2, p. 33

Efficacy Against Any HPV related CIN in MITT-3 Population

- In the MITT-3 population, the vaccine efficacy against all CIN was lower (10.9%, 95% CI: <0.0, 22.6%)than that observed in the RMITT-2 population, and again did not reach statistical significance. This is shown in Table 44 below.

TABLE 44
Protocol 015: Analysis of Efficacy Against CIN Irrespective of HPV Type (MITT-3 population)

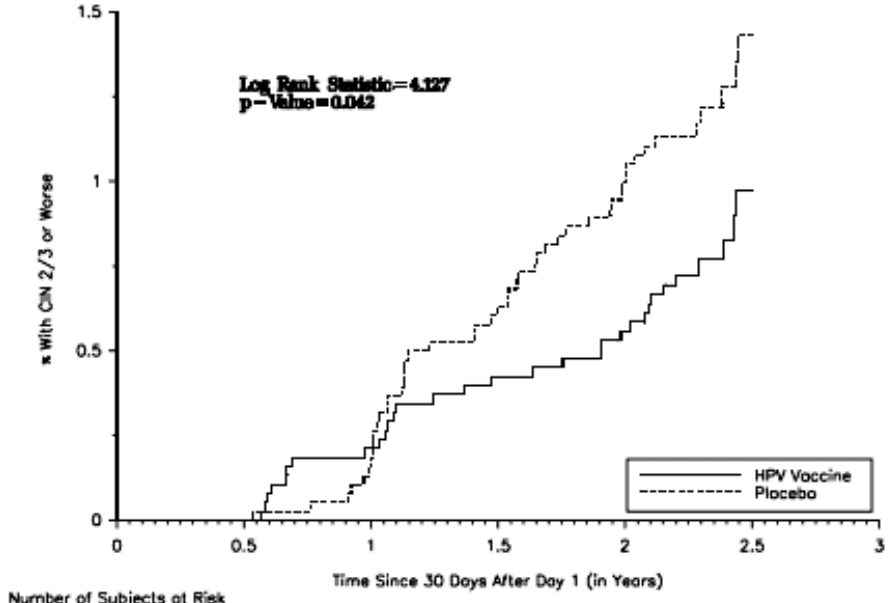
	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
CIN Due to any HPV type	5947	382	10954.1	3.5	5973	432	11038.4	3.9	**10.9%**	<0.0, 22.6%
CIN 1	5947	296	10999.6	2.7	5973	339	11079.4	3.1	**12.1%**	<0.0, 25.0%
CIN 2/3 or worse	5947	167	11121.7	1.5	5973	199	11216.7	1.8	**15.4%**	<0.0, 31.5%
CIN 2	5947	111	11140.5	1.0	5973	143	11234.7	1.3	**21.7%**	<0.0, 39.5%
CIN 3	5947	98	11158.8	0.9	5973	123	11249.0	1.1	**19.7%**	<0.0, 39.0%
AIS	5947	4	11176.9	0.04	5973	7	11267.5	0.1	**42.4%**	<0.0, 87.6%
Cervical cancer	5947	0	11178.0	0.0	5973	0	11267.9	0.0	**NA**	NA

Source: Table 11-97, CSR 015v2, p. 669 and Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2, p. 33

The sponsor also presented time to CIN 2/3 due to any HPV type through 2.5 years of follow-up in the RMITT-2 and MITT-3 populations. In the RMITT-2 population, there is a suggestion of a lower risk of developing CIN 2/3 or worse irrespective of HPV type in Gardasil recipients as compared to placebo recipients as time progresses (p-value = 0.042). (See Figure 7). There is less of a suggestion of benefit to the MITT-3 population against CIN 2/3 or worse irrespective of HPV type (p-value = .101). (See Figure 8). However, as noted earlier, not all subjects have been followed to the later time points, and we do not know the subject's PCR status for all oncogenic HPV types at baseline, and further follow-up is necessary before a definitive conclusion can be reached.

FIGURE 7
Protocol 015

Plot of Time to CIN 2/3 or Worse Diagnosis Through 2.5 Years of Follow-Up
(Restricted MITT-2 Population)



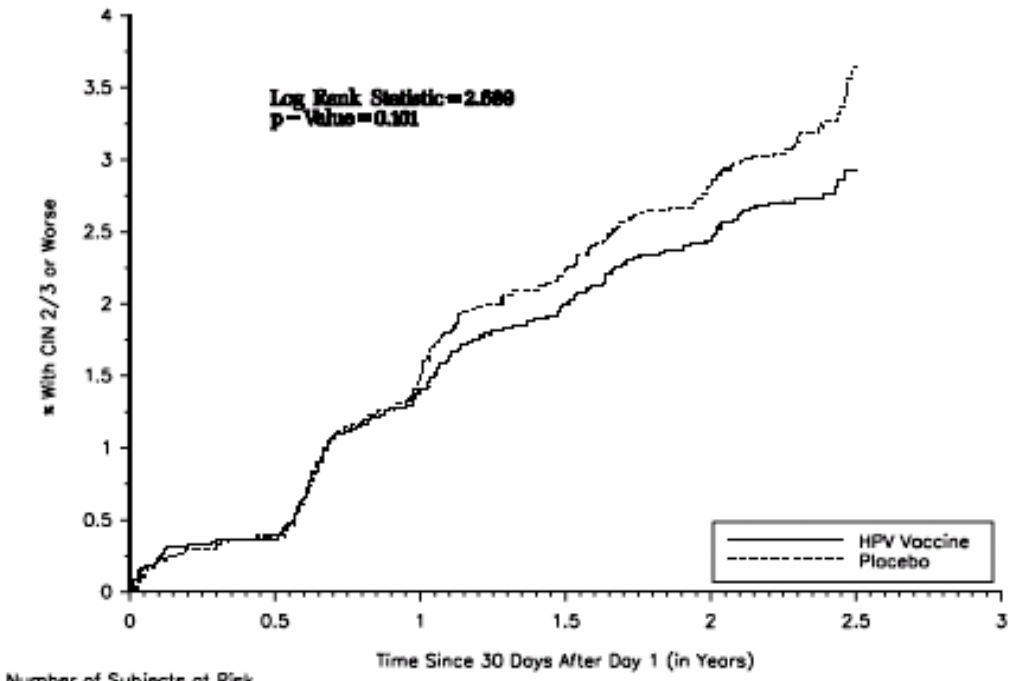
Number of Subjects at Risk

HPV Vaccine	3790	3785	3761	3746	3709	723	0
Placebo	3828	3825	3805	3784	3737	724	0

Source: Figure 11-6, CSR 015v2, p. 671

FIGURE 8
Protocol 015

Plot of Time to CIN 2/3 or Worse Diagnosis Through 2.5 Years of Follow-Up
(Modified Intention-to-Treat Population 3)



Number of Subjects at Risk

HPV Vaccine	5950	5908	5809	5753	5667	1085	0
Placebo	5976	5938	5835	5778	5681	1076	0

Source: Figure 11-7, CSR 015v2, p. 672

Exploratory Analyses of Vaccine Efficacy Against All EGLs

Analyses of Efficacy Against All External Genital Lesions in MITT-2 and MITT-3 Populations

- This analysis is conducted in the RMITT-2 population and the MITT-3 population. There is higher vaccine efficacy against any HPV related EGL (77.8%, 95% CI: 64.1, 86.9% in the RMITT-2 population and 47.6%, 95% CI: 29.8, 58.0% in the MITT-3 population) which reach statistical significance as compared to any HPV related CIN in both these populations noted above. (See Tables 45 and 46 below).

TABLE 45
Protocol 015: Analysis of Efficacy Against EGL by Severity Irrespective of HPV Type_ (Restricted MITT-2 population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
EGL Due to Any HPV type	3837	21	7144.5	0.3	3856	95	7168.8	1.3	**77.8%**	64.1, 86.9%
Condyloma, VIN 1 or VaIN 1	3837	20	7145.1	0.3	3856	84	7174.4	1.2	**76.1%**	60.7, 86.1%
VIN 2/3 or VaIN 2/3	3837	1	7161.2	0	3856	16	7216.9	0.2	**93.7%**	59.5, 99.8%
Vulvar or Vaginal Cancer	3837	0	7161.7	0	3856	0	7225.5	0	**NA**	NA

*Restricted MITT-2 population: Subjects were seronegative and PCR negative to all 4 vaccine HPV types and had a negative Pap test at Day 1. Cases were counted starting 30 days after dose 1.
Source: Table 7-13, CSR 015v2, p. 258

TABLE 46
Protocol 015: Analysis of Efficacy Against EGL by Severity Irespective of HPV Type Including Biopsies Outside the context of the study (MITT-3 population)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
EGL Due to Any HPV type	6016	96	11116.4	0.9	6027	177	11153.6	1.6	**47.6%**	29.8, 58.0%
Condyloma, VIN 1 or VaIN 1	6016	90	11122.6	0.8	6027	163	11163.0	1.5	**44.6%**	27.9, 57.6%
VIN 2/3 or VaIN 2/3	6016	9	11210.6	0.1	6027	24	11270.0	0.2	**62.3%**	16.0, 84.6%
Vulvar or Vaginal Cancer	6016	0	11217.4	0.0	6027	0	11286.4	0.0	**NA**	

Source: Table 11-99, CSR 015v2, p. 673

Exploratory Analyses of Efficacy Against All Cervicovaginal and External genital Disease (RMITT-2 and MITT-3 populations)

Exploratory analyses of efficacy against all cervicovaginal and external genital disease irrespective of HPV type were also conducted in the RMITT-2 and MITT-3 populations.

The point estimates of efficacy with 95% CIs lie between the point estimates for the separate lesion types. These are as noted in Table 47 below.

TABLE 47
Protocol 015: Analysis of Efficacy Against Cervicovaginal and External Genital Disease Irrespective of HPV Type

	Gardasil N=6082				Placebo N=6075					
Analysis Population	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
RMITT-2*	3839	125	7172.7	1.7	3858	213	7198.6	3.0	**41.1%**	26.2, 53.2%
MITT-3	6021	452	10952.6	4.1	6029	567	10990.8	5.2	**20.0%**	9.3, 29.5%

*RMITT-2 population: Subjects were seronegative and PCR negative to all 4 vaccine HPV types and had a negative Pap test at Day 1. Cases were counted starting at 30 days after dose 1.
Source: Table 7-14, CSR 015v2, p. 260

Exploratory Analyses of Disease due to Vaccine versus Non-Vaccine HPV Types
The incidence of CIN **not related** to vaccine HPV types was generally comparable between the vaccine and placebo groups, although there were slightly more cases not related to HPV 6/11/16/18 in the vaccine group as compared to the placebo group in analyses for cases of CIN, EGL, and both together. These analyses are shown in the RMITT-2 population in Table 48 below and the point estimates for efficacy do not reach statistical significance. The sponsor states that testing is being conducted for -- other HPV types, and will be available in an extension report in the future.

TABLE 48
Protocol 015: Analysis of Vaccine and Non-Vaccine HPV types in EGL, CIN, and EGL+CIN (RMITT-2 population)*

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
CIN Due to any HPV type	3789	112	7140.5	1.6	3826	141	7212.2	2.0	19.8%	<0.0, 38.0%
+6/11/16/18	3789	4	7192.2	0.1	3826	48	7269.4	0.7	91.6%	77.0, 97.8%
- 6/11/16/18	3789	111	7141.6	1.6	3826	105	7224.4	1.5	-6.9%	<0.0, 18.8%
EGL Due to any HPV type	3837	21	7144.5	0.3	3856	95	7168.8	1.3	77.8%	64.1, 86.9%
+6/11/16/18	3837	4	7157.3	0.1	3856	84	7179.2	1.2	95.2%	87.3, 98.7%
- 6/11/16/18	3837	18	7147.4	0.3	3856	15	7214.4	0.2	-21.1%	<0.0, 42.4%
CIN and EGL Due to any HPV type	3839	125	7172.7	1.7	3858	213	7198.6	3.0	41.1%	26.2, 53.2%
+6/11/16/18	3839	8	7247.4	0.1	3858	119	7268.9	1.6	93.3%	86.3, 97.2%
- 6/11/16/18	3839	121	7177.0	1.7	3858	116	7261.2	1.6	-5.5%	<0.0, 18.9%

*RMITT-2 population: Subjects were seronegative and PCR negative to all 4 vaccine HPV types and had a negative Pap test at Day 1. Cases were counted starting 30 days after dose 1.
Source: From Tables 7-15, 7-16, 7-17, CSR 015v2, p. 262-4

Exploratory Analysis of Impact on Pap Test Abnormalities

- As noted in Table 49 below, the impact on Pap test abnormalities in both the RMITT-2 and MITT-3 populations was small in each population for the specific diagnoses.

TABLE 49
Protocol 015: Impact of Vaccination on Pap Test Abnormalities (RMITT-2 and MITT-3 Populations)

Population	**Vaccine Efficacy**	**95% CI**
RMITT-2		
ASC-US or worse	**8.1%**	**<0.0, 16.7%**
ASC-US with + HPV probe	**27.8%**	**0.9, 47.7%**
LSIL	**14%**	**2, 24.5%**
MITT-3		
ASC-US or worse	**4.4%**	**<0.0, 10.6%**

Source: From Table 7-18, CSR 015v2, p. 266 and Table 11-100, p. 674

Exploratory Analysis of Impact on Gynecological Procedures
There is evidence of a modest reduction of any gynecological procedures in the RMITT-2 population (21%, 95% CI: 7.9, 32.3%) and a lesser impact in the MITT-3 population (9.9%, 95% CI: 1.6, 17.6%). There is a higher point estimate of efficacy for any EGL procedure in both the RMITT-2 population (54.7%, 95% CI: 37.3, 67.7%) and MITT-3 population (31.5%, 95% CI: 16.2, 44.2%) as compared to those for cervical procedures. (See Table 50 below).

TABLE 50
Protocol 015: Impact of Vaccination on Gynecologic Procedures
(RMITT-2 and MITT-3 Populations)

Population	Vaccine Efficacy	95% CI
RMITT-2		
Any gyn procedure	**21%**	**7.9, 32.3%**
EGL procedure	**54.7%**	**37.3, 67.7%**
Cervical procedure	**13.1%**	**<0.0, 26.4%**
MITT-3		
Any gyn procedure	**9.9%**	**1.6, 17.6%**
EGL procedure	**31.5%**	**16.2, 44.2%**
Cervical procedure	**6.7%**	**<0.0, 15.0%**

(Source: From Table 7-19, CRS 015v2, p. 268, andTable 11-101, CSR 015v2, p. 675

Exploratory Analysis of Efficacy for HPV 6/11/16/18 related CIN in <u>non-naïve</u> subjects (seropositive <u>and/or</u> PCR positive at Day 1 to relevant vaccine HPV type)
These exploratory analyses were conducted to evaluate the therapeutic efficacy of Gardasil. The sponsor presented data for subjects who were PCR positive and seronegative, and PCR negative and seropositive. Further analyses were requested for all subgroups. These analyses were conducted on subgroups of the non-naïve population.

Subjects who were PCR positive <u>and/or</u> seropositive for the relevant HPV type at baseline

- In an analysis of efficacy against vaccine HPV related CIN in this subgroup, the point estimate of vaccine efficacy was low (18.9%), and did not reach statistical significance (95% CI: <0.0, 38.6%). (See Table 51 below)

TABLE 51
Protocol 015: Analysis of Efficacy Against Vaccine HPV Type Related CIN at Day 1 Among Subjects who were PCR Positive and/or Seropositive for the Relevant HPV Type at Day 1

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	1575	96	2862.8	3.4	1598	120	2903.5	4.1	18.9%	(<0.0, 38.6%)
CIN 2 or worse	1575	67	2887.8	2.3	1598	83	2942.4	2.8	17.8%	(<0.0, 41.3%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0019, Additional Efficacy Analyses Requested by CBER, submitted 4/7/06, Table 1e-3, p. 14

Subjects who were PCR negative and seropositive for the relevant HPV type at baseline

- There was a small number of cases of HPV 6, 11, 16, 18 related CIN in these subjects in the placebo group and none in the Gardasil group. The point estimate of the vaccine efficacy was 100% but did not reach statistical significance. (See Table 52 below).

Reviewer's Comment: The Sponsor has speculated that subjects who are seropositive and PCR negative have cleared their infection. They presumably do not have "prevalent" disease.

TABLE 52
Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 related CIN or Worse Among Subjects who were PCR Negative and Seropositive for the Relevant HPV type(s) at baseline

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	834	0	1554.3	0.0	866	3	1627.2	0.2	100%	(<0.0, 100%)
CIN 2 or worse	834	0	1554.3	0.0	866	3	1627.2	0.2	100%	(<0.0, 100%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0019, Additional Efficacy Analyses Requested by CBER, submitted 4/7/06, Table 1d-2, p. 9

Subjects who were PCR positive and seronegative for the relevant HPV type at baseline

- There was a slight reduction in the incidence rate in HPV 16/18 related CIN 2/3 or worse in this population (27.4%), although not reaching statistical significance (95% CI: < 0.0, 58.6%). See Table 53 below. The greatest reduction was seen in HPV 18 related CIN 2/3 or worse, possibly related in part to the lower prevalence of HPV 18.

TABLE 53
Protocol 015: Analysis of Efficacy Against HPV 16/18 related CIN 2/3 or Worse Among Subjects who were Seronegative and PCR Positive for the Relevant HPV type at Day 1 – (Cases counted starting at 30 days postdose 1)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN 2/3 or Worse	422	25	769.8	3.2	401	33	737.3	4.5	**27.4%**	<0.0, 58.6%
BY HPV Type										
HPV 16 Related CIN 2/3 or Worse	286	24	516.2	4.6	266	26	492.1	5.3	**12.0%**	<0.0, 51.6%
HPV 18 Related CIN 2/3 or Worse	164	1	302.6	0.3	163	8	298.6	2.7	**87.7%**	8.0, 99.7%

Source: Table 7-20, CSR 015v2, p. 271

- For this same subgroup (seronegative, PCR positive), there was also a 27.4% reduction in HPV 6/11/16/18 related CIN, but again without statistical significance [95% CI: <0.0, 52.2%]. (Source: Table 11-102, CSR 015v2, p. 676, not shown here)

Subjects who were PCR positive and seropositive for the relevant HPV type at baseline

- There was a slight reduction in the incidence of HPV 6, 11, 16, 18 related CIN in the Gardasil group as compared to placebo, but this did not reach statistical significance. (See Table 54 below).

TABLE 54

Protocol 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN or AIS Among Subjects who were Seropositive and PCR Positive for the Relevant HPV Type at Day 1

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	398	54	693.8	7.8	430	63	746.6	8.4	7.8	(<0.0, 37.1%)
CIN 2 or worse	398	42	703.0	6.0	430	48	760.2	6.3	5.4	(<0.0, 39.0)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0019, submitted 4/7/06, Efficacy Information Amendment, Table 1a-1, p. 2

- A similar exploratory analysis of efficacy against HPV 16/18 related CIN 2/3 or worse in this subgroup. Overall, the incidence of HPV 16/18 related CIN 2/3 or worse cases was the same in the Gardasil and placebo groups (8.0 in each group). (See Table 55 below.)

TABLE 55
Protocol 015: Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse Among Subjects who were Seropositive and PCR Positive for the Relevant* HPV Type at Day 1 – (Cases Counted Starting at 30 days Postdose 1)

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN 2/3 or Worse	297	41	512.2	8.0	333	46	576.7	8.0	-0.4%	<0.0, 35.8%
HPV 16 Related CIN 2/3 or Worse	240	37	408.1	9.1	268	44	455.1	9.7	6.2%	<0.0, 41.1%
HPV 18 Related CIN 2/3 or Worse	62	4	112.5	3.6	72	2	133.3	1.5	-137.1%	<0.0, 66.0%

*Relevant HPV type=vaccine HPV type with which the subject is sero and PCR positive at Day 1
Source: Additional Efficacy Analyses requested by CBER 3/06, Ref. 5.3.5.1, P015v2, p. 37

Reviewer's Comment: Although administration of Gardasil to subjects who were seropositive and PCR positive at baseline in Study 015 did not appear to be associated wiith an increased incidence of cervical disease in the Gardasil group as compared to the placebo group, the results in Study 013 and the combined analyses raised a concern for the review team. In Study 013 and the combined analysis, there was a higher incidence of Gardasil recipients with squamous intraepithelial lesion as compared to placebo recipients in this subgroup. The findings in Study 013 may be related to the presence of an abnormal Pap test at baseline. Please see discussion of non-naïve subjects (seropositive and PCR positive) in Study 013 and in the overall efficacy section.

Similar analyses were conducted for vaccine HPV type related EGLs in the non-naïve subgroup. These exploratory analyses are included below.

Exploratory Analysis of Efficacy for HPV 6, 11, 16, or 18 related EGLs in <u>non-naïve</u> subjects (seropositive <u>and/or</u> PCR positive at Day 1 to relevant vaccine HPV type)

Subjects who were PCR negative and seropositive for the relevant HPV type at baseline

The sponsor provided an exploratory analysis of efficacy in subjects who were PCR negative and seropositive at Day 1 for the relevant vaccine HPV type. All cases in this subgroup occurred in the placebo group and none in the Gardasil group. The point estimate of vaccine efficacy was 100%, but did not reach statistical significance. (This result was similar to that seen for efficacy against vaccine HPV type related CIN in Study 015). (See Table 56 below).

TABLE 56
Protocol 015: Analysis of Efficacy Against Vaccine HPV Type Related EGLs Among Subjects who were PCR Negative and Seropositive for the Relevant Vaccine HPV Type(s) at Day 1

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related EGL	843	0	1564.3	0.0	874	4	1635.7	0.2	100%	(<0.0, 100%)
Condyloma, VIN 1, or VaIN 1	843	0	1564.3	0.0	874	4	1635.7	0.2	100%	(<0.0, 100%)
VIN 2/3 or VaIN 2/3	843	0	1564.3	0.0	874	0	1638.9	0.0	NA	NA

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 2e-3, Efficacy Amendment 3/22/06, p. 40

Subjects who were PCR positive and seronegative for the relevant HPV type at baseline

- Incidence rates were comparable between treatment groups in this subgroup analysis. (See Table 57 below).

TABLE 57
Protocol 015: Analysis of Efficacy Against Vaccine HPV Type Related EGLs Among Subjects who were PCR Positive and Seronegative for the Relevant Vaccine HPV Type(s) at Day 1

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related EGL	553	27	997.6	2.7	543	25	985.9	2.5	-6.7%	(<0.0, 40.4%)
Condyloma, VIN 1, or VaIN 1	553	26	998.8	2.6	543	24	987.3	2.4	-7.1%	(<0.0, 40.9%)
VIN 2/3 or VaIN 2/3	553	3	1031.1	0.3	543	2	1014.4	0.2	-47.6%	(<0.0, 83.1%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 2e-6, Additional Efficacy Analyses, 3/22/06, p. 42

Subjects who were PCR positive and seropositive for the relevant HPV type at baseline

- There was no difference in the incidence related rates of vaccine type HPV related EGLs overall between the Gardasil and placebo groups. There were few cases noted in either treatment group, and none of the point estimates reached statistical significance. (See Table 58 below).

TABLE 58
Protocol 015: Analysis of Efficacy Against Vaccine HPV Type Related EGLs Among Subjects who were PCR Positive and Seropositive for the Relevant Vaccine HPV Type(s) at Day 1

	Gardasil N=6082				Placebo N=6075					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related EGL	403	7	745.0	0.9	433	7	802.2	0.9	-7.7	(<0.0, 67.8%)
Condyloma, VIN 1, or VaIN 1	403	6	746.8	0.8	433	7	802.2	0.9	7.9	(<0.0, 74.4%)
VIN 2/3 or VaIN 2/3	403	1	753.9	0.1	433	0	811.9	0.0	NA	NA

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 2e-9, Additional Eficacy Analysis, 3/22/06, P. 44

Reviewer's Comment: There was no apparent evidence of efficacy against vaccine HPV type related EGLs in subjects who were non-naïve to a vaccine HPV type (seropositive and/or PCR positive). However, these exploratory analyses were also conducted in Study 013 and in the combined analysis. The results were similar in these analyses. Please see Study 013 and the overall efficacy section for these results and discussions.

Safety Outcomes

Safety population: All subjects who received at least one dose of vaccine or placebo were followed for safety.

Safety Cohorts

- **Detailed Safety Cohort (US):** Subjects enrolled in the United States also underwent a comprehensive collection of nonserious adverse experiences using a VRC. For the purposes of this CSR, this cohort is called the Detailed Safety Cohort (US). In this cohort, each subject recorded her Temperature 4 hours after vaccination and for 4 days thereafter on a VRC. Any systemic AE or injection site AE for Days 1-14 after each vaccination were recorded on the VRC as well.
- **Detailed Safety Cohort (UK):** Subjects in the UK were solicited for NSAEs via questioning at the next visit. A VRC was not utilized. This cohort = General Safety Cohort (UK).
- **General Safety Cohort:** NSAEs in the other countries could have been reported at the discretion of the investigator. These were captured for 14 days after each vaccination. This cohort is called the General Safety Cohort (non-US and non-UK study sites).

TABLE 59
Protocol 015: Clinical Adverse Experience Summary (Days 1-15 Following Any Vaccination Visit) – All Vaccinated Subjects

	Gardasil N=6075	Placebo N=6076
Subjects with follow-up	6019	6031
Subjects with SAE	17 (0.3%)	16 (0.3%)
Subjects who died	2 (0.03%)	0 (0.0%)
Subjects who discontinued due to AE	6 (0.1%)	4 (0.1%)
Subjects who discontinued due to an SAE	2 (0.03%)	1 (0.02%)

Source: Table 8-1, CSR 015v2, p. 289

TABLE 60
Protocol 015: Clinical Adverse Experience Summary: Days 1-15 Following Any Vaccination Visit -Detailed Safety Cohort (US)

	Gardasil N=457	Placebo N=454
Subjects with follow-up	448	447
Subjects with $\geq$ 1 AE	409 (91.3%)	395 (88.4%)
Subjects with $\geq$ 1 IS AE	379 (84.6%)	349 (78.1%)
Subjects with $\geq$ 1 systemic AE	271 (60.5%)	266 (59.5%)
Subjects with SAE	1 (0.2%)	0 (0.0%)
Subjects who died	1 (0.2%)	0 (0.0%)
Subjects who discontinued due to AE	3 (0.7%)	0 (0.0%)
Subjects who discontinued due to an SAE	1 (0.2%)	0 (0.0%)

Source: Table 8-2, CSR 015v2, p. 291

Overall Adverse Events

- Slightly more subjects in the vaccine group experienced one or more AEs compared to the placebo group.
- There were somewhat more injection site AEs in the vaccine group compared to the placebo group, although the rates of systemic AEs were similar in both groups.
- Few subjects discontinued due to an AE.
- One subject experienced an SAE within 15 days of any vaccination visit. (See listing of SAEs.)

Adverse Events by Dose in Detailed Safety Cohort (US) (See Table 61 below.)

- Regarding the 15 days after Vaccination 1, 2 and 3 in the US cohort, the proportions of subjects with injection site and systemic adverse events were similar in the vaccine and placebo groups after Dose 1, but there were more injection site AEs in the vaccine group compared to the placebo group after Doses 2 and 3 (app. 60% versus 49%).
- Few subjects discontinued due to an adverse event, and there was one subject with an SAE in the vaccine group after dose 3 who discontinued due to the SAE.

TABLE 61
Protocol 015: Clinical Adverse Event Experience after Dose 1, Dose 2, and Dose 3
Days 1-15 after vaccination (Detailed Safety Cohort, US)

	Vaccine	Placebo
After Dose 1	N=457	N=454
With one or more AE	351 (78.5%)	344 (77%)
Injection site AE	285 (63.8%)	277 (62%)
Systemic AE	197 (44.1%)	216 (48.3%)
After Dose 2	N=446	N=446
With one or more AE	296 (67.6%)	251 (57.6%)
Injection site AE	264 (60.3%)	212 (48.6%)
Systemic AE	111 (25.3%)	104 (23.9%)
After Dose 3	N=433	N=435
With one or more AE	296 (69.3%)	245 (56.7%)
Injection site AE	272 (63.7%)	211 (48.8%)
Systemic AE	107 (25.1%)	101 (23.4%)

Source: From Tables 11-107, 11-108, 11-109, CSR 015v2, p. 699-704

Adverse Events by Baseline Serostatus and PCR Status (See Table 62 below.)

- There was a higher proportion of Gardasil seronegative and PCR negative subjects with systemic AEs as compared to Gardasil recipients who were seropositive or PCR positive at baseline, although there were similar differences between the two placebo groups (who received the same placebo), thus the clinical significance of these differences is uncertain.

TABLE 62
Protocol 015: Clinical Adverse Events in those who were Seronegative and PCR Negative at Baseline, and in those who were Seropositive or PCR positive at Baseline (after any Vaccination, and after Doses 1, 2, and 3, Days 1-15)
(Detailed Safety Cohort, US)

	Seronegative and PCR Negative		Seropositive or PCR positive	
	Vaccine N=318	Placebo N=333	Vaccine N=133	Placebo N=116
After any injection				
With one or more AE	288 (92.3%)	295 (89.9%))	116 (89.2%)	96 (84.2%)
Injection site AE	269 (86.2%)	264 (80.5%)	107 (82.3%)	81 (71.1%)
Systemic AE	199 (63.8%)	198 (60.4%)	67 (51.5%)	64 (56.1%)
After Dose 1	N=318	N=333	N=133	N=116
With one or more AE	249 (80.1%)	263 (80.2%)	97 (74.6%)	77 (67.5%)
Injection site AE	202 (65.0%)	214 (65.2%)	80 (61.5%)	59 (51.8%)
Systemic AE	138 (44.4%)	163 (49.7%)	55 (42.3%)	49 (43.0%)
After Dose 2	N=311	N=327	N=129	N=114
With one or more AE	215 (70.7%)	192 (60.0%)	80 (62.0%)	56 (50.5%)
Injection site AE	198 (65.1%)	166 (51.9%)	65 (50.4%)	43 (38.7%)
Systemic AE	82 (27.0%)	80 (25.0%)	29 (22.5%)	24 (21.6%)
After Dose 3	N=301	N=319	N=127	N=111
With one or more AE	207 (69.7%)	196 (61.8%)	86 (68.8%)	48 (43.6%)
Injection site AE	192 (64.6%)	173 (54.6%)	79 (63.2%)	37 (33.6%)
Systemic AE	83 (27.9%)	78 (24.6%)	21 (16.8%)	23 (20.9%)

Source: From Tables 11-110-117, CSR 015v2, p. 705-20

Intensities of AEs in Detailed Safety Cohort (US)

- The maximum intensity of any AE was mild or moderate for the majority of subjects.
- Similar proportions of subjects with a severe injection site AE in the vaccine (13.2%) and placebo (13.0%) group. (Source: Table 8-3, CSR 015v2, p. 293, not shown here)

Injection Site Adverse Events in the Detailed Safety Cohort (Days 1-5 after vaccination)

Specific Injection Site Adverse Events (See Table 63 below.)

- The most common injection site AE was pain, followed by erythema and swelling.
- The proportions of subjects with most specific injection site AEs were somewhat higher in the vaccine group as compared to the placebo group (except for injection site hemorrhage and pruritus).
- There was a statistically significant higher incidence of **pain** in the vaccine group as compared to the placebo group

TABLE 63
Protocol 015: Number (%) of Subjects with Injection Site AEs (≥ 1%) and Risk Differences Days 1-5 after any Vaccination Visit – Detailed Safety Cohort US)

	Vaccine	Placebo	Risk Difference Vaccine – Placebo (95% CI)	p-value
Number of subjects	457	454		
Subjects with follow-up	448	447		
Number (%) with one or more Injection Site AE	378 (84.4%)	348 (77.9%)	6.5% (1.4, 11.7%)	
Injection site pain	372 (83.0%)	339 (75.8%)	7.2 % (1.9, 12.5%)	**0.008**
Injection site erythema	137 (30.6%)	117 (26.2%)	4.4% (-1.5, 10.3%)	0.144
Injection site swelling	95 (21.2%)	75 (16.8%)	4.4% (-0.7, 9.6%)	0.092
Injection site hemorrhage	20 (4.5%)	22 (4.9%)	-0.5% (-3.4, 2.4%)	
Injection site pruritus	8 (1.8%)	13 (2.9%)	-1.1 % (-3.3, 0.9)	

Source: From Tables 8-6 and 8-7, CSR 015v2, p. 296-7

Injection site AEs post doses 1, 2, 3

- For the placebo group, the proportion of subjects with injection site AEs was somewhat higher after dose 1 as compared to the other doses, and the injection site AEs were similar across all doses for the vaccine group. (Source: Tables 11-122-124, CSR 015v2, p. 729-31, not shown here)

Injection site AEs and baseline serostatus and PCR status (See Table 64 below.)

- The proportions of subjects with an injection site AE in the US Detailed Safety cohort were similar when comparing baseline serostatus and PCR status.

TABLE 64
Protocol 015: Number (%) of subjects with Injection site AEs (Incidences ≥ 1%) Days 1-5 after any vaccination with Gardasil: Seronegative and PCR Negative, and Seropositive or PCR Positive (Detailed Safety Cohort, U.S)

	Seronegative and PCR Negative Detailed Safety Cohort US	Seropositive or PCR positive Detailed Safety Cohort US
Number of subjects	318	133
Subjects with follow-up	312	130
Number (%) with 1+ IS AE	268 (85.9%)	107 (82.3%)
Injection site pain	265 (84.9%)	104 (80.0%)
Injection site erythems	97 (31.1%)	40 (30.8%)
Injection site swelling	72 (23.1%)	23 (17.7%)

Source: From Tables 11-125, p. 732-3 and Table 11-129, p. 739-40, CSR 015V2

Intensities of Injection site AEs

- There was a higher proportion of subjects in the vaccine group who reported an injection site reaction with a maximum rating of moderate (24.3%) as compared to the placebo group (15.9%) within 5 days of vaccination. (Source: Table 8-8, CSR 015v2, p. 299, not shown here)
- After doses 1, 2, and 3, there was also a higher proportion of vaccine recipients with a moderate injection site AE as compared to placebo recipients. (Source: Tables 11-134-137, CSR 015v2, p. 747-54, not shown here) (Note: The percentages of subjects with a specific grade AE are based on the total number of subjects with follow-up).

Systemic AEs in Detailed Safety Cohort (Days 1-15 after vaccination)
Systemic AEs

- In both the vaccine and placebo groups, the most common clinical adverse experiences were headache, nasopharyngitis, and nausea.
- For most specific systemic AEs, the rates are comparable between the 2 groups. Differences were noted in both directions. Seasonal allergy were more often reported in the vaccine group in the 15 days after any vaccination visit (2.2% in vaccine versus 0.4% in placebo, risk difference 1.8 (0.3, 3.7). (See Table 65 below).

TABLE 65
Protocol 015: Number (%) of Subjects with Most Common Systemic AEs (Days 1-15 after any vaccination visit) (Detailed Safety Cohort) with Risk Differences

	Vaccine	Placebo	Risk Difference Vaccine – Placebo (95% CI)
Number of subjects	457	454	
Subjects with follow-up	448	447	
Number (%) with one or more systemic AE	217 (60.5%)	266 (59.5%)	
Headache	111 (24.8%)	112 (25.1%)	-0.3 (-6, 5.4)
Nasopharyngitis	43 (9.6%)	31 (6.9%)	2.7 (-1, 6.4)
Nausea	38 (8.5%)	31 (6.9%)	1.5 (-2, 5.1)
Pharyngolaryngeal Pain	25 (5.6%)	29 (6.5%)	-0.9 (-4.1, 2.3)
Upper abdominal Pain	21 (4.7%)	22 (4.9%)	-0.2 (-3.2, 2.7)
Dysmenorrhea	20 (4.5%)	24 (5,4%)	-0.9 (-3.9, 2)
Pyrexia	20 (4.5%)	18 (4.0%)	0.4 (-2.3, 3.2)
Diarrhea	18 (4.0%)	18 (4.0%)	0 (-2.7, 2.7)
Fatigue	16 (3.6%)	27 (6.0%)	-2.5 (-5.4, 0.3)
Back Pain	13 (2.9%)	24 (5.4%)	-2.5 (-5.3, 0.1)

Source: From Tables 8-11 and 8-12, CSR 015v2, p. 303-12

Systemic AEs after Doses 1, 2, and 3

- For both vaccination groups, systemic AEs were more often seen after dose 1 as compared to doses 2 and 3. (Source: Tables 11-143-45, CSR 015v2, p. 778-87, not shown here).

Systemic AEs and baseline serostatus and PCR status

- The proportions of subjects who reported systemic AEs within these subgroups were generally comparable to those reported in the entire Detailed Safety Cohort after each dose, although the comparisons are limited by the small number of subjects. (Source: Tables 146-53, CSR 015v2, p. 788-822, not shown here)

Systemic AE of interest

- Per Table 11-160 in the CSR for Study 015v2, one subject from the General Safety Cohort (AN42548) developed **polyarthritis** 21 days after the 1st dose of vaccine. This was considered a NSAE, was described as moderate in intensity, and was a continuing problem. (Site 015-89) Additional information was requested on this subject, and on follow-up she was diagnosed as having Carpal Tunnel syndrome and was scheduled to undergo corrective surgery.

Temperature Elevations Days 1-5 in the Detailed Safety Cohort

- The proportions of subjects with a temperature elevation were similar in the vaccine and placebo groups. (See Table 66 below).

TABLE 66
Protocol 015: Number (%) of Subjects with Elevated Temperatures by Vaccination Visit (Day 1-5 after any Vaccination Visit) (Detailed Safety Cohort US)

	Gardasil N=457	Placebo N=454
Subjects with follow-up	443	446
Maximum T (Oral)		
<37.8 °C (< 100 °F) or normal	429 (96.8%)	431 (96.6%)
≥ 37.8 °C (≥ 100°F) and < 38.9 °C (< 102 ° F) or abnormal	13 (2.9%)	14 (3.1%)
≥ 38.9 °C (≥ 102°F) and < 39.9 °C (< 103.8 ° F)	1 (0.2%)	1 (0.2%)
≥ 39.9 °C (≥ 103.8°F) and < 40.9 °C (< 105.6 ° F)	0 (0.0%)	0 (0.0%)
≥ 40.9 °C (≥ 105.6°F)	0 (0.0%)	0 (0.0%)

Percentages are calculated based on the number of subjects with follow-up.
N= number of subjects who received only the clinical material in the given column.
Source: Table 8-15, CSR 015v2, p. 317

Significant/Potentially Significant Events

Deaths (See Table 67 below.)

- There were 9 deaths (5 in the vaccine groupand 4 in the placebo group). (None were considered by the investigator to be vaccine related.)

TABLE 67
Protocol 015: Deaths in Gardasil and Placebo Recipients

AN	Event	Days Post Dose	Duration
GARDASIL Recipients (5)			
44256	Probable urosepsis with pregnancy DIC, Multiorgan failure	358 days postdose 3	2 days
44507	DVT, PE	19 days postdose 1	2 days
47711	Seizure, drug use	4 days postdose 3	1 day
46973	Multiple trauma post MVA	8 days postdose 2	1 day
55537	Multiple trauma in MVA	90 days postdose 3	1 day
PLACEBO Recipients (4)			
40127	Suicide	517 days postdose 3	1 day
40793	Suicide	200 days postdose 3	1 day
46856	Multiple trauma post MVA	342 days postdose 3	1 day
56248	Asphyxia 4 days post-C-section	256 days postdose 3	1 day

Source: CSR 015v2, Table 8-17, p. 321-322

- Case summaries of deaths excluding trauma in Gardasil recipients from Table 67 above.
  - **AN 44256: (Study Site 015021, Peru):** This subject had a biopsy 2 months before the death due to suspected urosepsis early in pregnancy; the CIN 2 and condyloma noted were negative for the 4 vaccine HPV types.
  - **AN44507: (Study Site 015019, Denmark):** This 22 year old non-smoking white female subject had symptoms of leg pain prior to the vaccination (11/15/02), and

was seeing a masseur for this complaint. She was also on hormonal contraceptives. The subject was vaccinated with her first dose of Gardasil on -------. On --------, Day 19 Postdose 1, the subject experienced suspected deep vein thrombophlebitis (DVT) of the left leg and consulted her own general practitioner. On --------, Day 20 Postdose 1, the subject experienced severe chest pain and was taken to the emergency room (ER). The subject subsequently experienced a suspected acute massive pulmonary embolism of severe intensity and was admitted to the intensive care unit (ICU). Echocardiography was performed and showed normal aorta and no thrombosis in the vena cava. Abdominal ultrasound was performed with no abnormal findings. On the same day, the subject died of acute massive pulmonary embolism and deep vein thrombosis of the left leg. The autopsy report confirmed the diagnosis of acute massive pulmonary embolism and deep thrombophlebitis of the left leg and also revealed an incidental finding of acute ischemic renal failure.

- **AN 47711 (Study Site 015010):** This subject had a history of seizure disorder and anxiety. She suffered a seizure 4 days after dose 3, and was noted to have cocaine in her urine.

Serious Adverse Events

- Upon review of Table 8-18 (CSR 015v2, p. 325-30, not shown here), there were **43 vaccinees listed with serious adverse events, and 52 placebo recipients listed with serious adverse events.** The WAES reports for these subjects were reviewed.
- The most common serious adverse experiences in both vaccination groups were pregnancy related (for example, premature labor, prolonged delivery requiring intervention). The incidences of these events were generally comparable between the 2 vaccination groups.
- The most common non-pregnancy-related serious adverse experiences were infections and gastrointestinal complaints. The incidences of these events were generally comparable between the 2 vaccination groups.
- Table 68 below includes the SAEs in Gardasil recipients (excluding deaths, shown in Table 67, and excluding OB-GYN condition, shown in Table 69).

TABLE 68
Protocol 015: SAEs in Gardasil Recipients in Protocol 015
(Excluding Deaths and Ob-GYN Conditions)

AN	Event	Days Post dose Gardasil	Duration	Outcome	Action
COAGULATION					
AN 47277	Thrombophlebitis (severe) – also on OCPs	4 days postdose 2	15 days	Recovered	None
GI					
AN 57028	Gastroenteritis (severe)	5 days postdose 2	15 days	Recovered	None
AN 54002	Gastroenteritis (severe)	13 days postdose 3	5 days	Recovered	None
AN 54010	Reflux espohagitis (severe)	2 days postdose 1	4 days	Recovered	None
AN 45992	Cholelitiasis (severe)	3 days postdose 2	6 days	Recovered	None
AN 45930	Appendicitis (mild)	42 days postdose 2	3 days	Recovered	None
AN 42410 (dup in OB-GYN)	Appendicitis (severe)	183 days postdose 3	4 days	Recovered	None
INFECTION					
AN 45935	Pneumonia, mild	5 days postdose 1	13 days	Recovered	None
MUSCULOSKELETAL					
AN 55101	Injection site pain and adjacent joint pain, and decreased movement (moderate)	1 day postdose 2	5.09 months	Recovered	None
NEURO					
AN 40007	Dizziness (severe)	5 days postdose 2	7 days	Recovered	None
AN 45384	Headache (severe)	2 days postdose 3	8 days	Recovered	None
PSYCH					
AN 57846	Bipolar disorder (moderate)	105 days postdose 3	7 days	Recovered	None
RESP.					
AN 49456	URI, sinusistis, and severe asthma History allergies	9 days postdose 2	3 days	Recovered	None
RHEUM/IMMUNE					
AN 42366	Cutaneous vasculitis Labs: ANCA normal, ANA neg., anti-CL neg.	10 days postdose 3	1.35 months	Recovered	None

Source: From Table 8-18, CSR 015v2, p. 327-30

- Subject AN 42366 with leukocytoclastic vasculitis experienced cold fingers and cyanotic feet and toes of moderate intensity app. 10 days postdose 3. The subject was seen by a rheumatologist. Her tests (as noted in Table 68 above) were normal, including a CXR. She was treated with prednisolone and recovered. A follow up

WBC showed a slightly elevated WBC [10.2 x 10(9)/L, with a normal WBC of 3-9 x 10(9)]. She was discontinued from the prednisilone and recovered. Follow-up blood tests were normal. The event lasted 1.35 months.

TABLE 69
Protocol 015: Serious Ob-GYN Adverse Events (excludes deaths)

OB/GYN	SAE	Time postdose	Duration	Outcome	Action Taken
AN 43708	Ovarian cysts (moderate)	12 days postdose 2	1 day	Recovered	None
AN 47934	Ovarian cysts (severe)	14 days postdose 2	4 days	Recovered	None
AN 56349	Headache (severe)	1 day postdose 3	5 days	Recovered	None
	Hypertension (severe)	1 day postdose 3	1 day	Recovered	None
	Preeclampsia (moderate)	260 days postdose 3	2 days	Recovered	None
	Oligohydramnios (mild)	261 days postdose 3	3 days	Recovered	None
AN 40391	Failed trial of labor (moderate)	286 days postdose 1	5 days	Recovered	None
AN 42410 (dup in GI)	Failed trial of labor (severe)	261 days postdose 3	15 hours	Recovered	None
AN 40149	Failed trial of labor (severe)	268 days postdose 1	1 day	Recovered	None
AN 47581	Hyperemesis gravidarum	37 days postdose 1	4 days	Recovered	None
	Hyperemesis gravidarum	53 days postdose 1	2 days	Recovered	None
AN 41060	Hyperemesis gravidarum (moderate)	42 days postdose 3	3 days	Recovered	None
	Fetal distress syndrome (severe)	284 days postdose 3	1 hr.	Recovered	
AN 45915	Endometritis (moderate)	116 days postdose 1	6 days	Recovered	None
AN 44276	Cervicitis (moderate)	230 days postdose 2	3 days	Recovered	None
AN 49548	Premature labor (moderate)	161 days postdose 1	8 hours	Recovered	None
	Fetal distress syndrome (moderate)	247 days postdose 1	3 days	Recovered	None
AN 48741	Premature labor	277 days postdose 3			
AN 48154	Premature Labor (severe)	231 days postdose 3	1 day	Recovered	None

[TABLE 69 (Cont.)] Protocol 015: Serious Ob-GYN Adverse Events (excludes deaths)

OB/GYN	SAE	Time postdose	Duration	Outcome	Action Taken
AN 41651	Pregnancy induced hypertension (moderate)	316 days postdose 2	3 days	Recovered	None
AN 57856	Pregnancy induced hypertension (moderate)	243 days postdose 2	8 days	Recovered	None
AN 48349	Postprocedural hemorrhage (mild)	1 day postdose 2	10 hours	Recovered	None
AN 42685	Threatened abortion (moderate)	25 days postdose 2	2 days	Recovered	None
AN 55561	Threatened abortion (mild)	45 days postdose 1	2.14 months	Recovered	None
AN 54573	Threatened abortion (moderate)	63 days postdose 1	CONT	Not recovered	None
AN 42471	Failed forceps delivery (severe)	413 days postdose 2	13 hours	Recovered	None
AN 43659	Abdominal pain Uterine contraction	94 days postdose 2 217 days postdose 2	1 day 3 days	Recovered Recovered	None None
AN 44134	Ectopic pregnancy (severe)	61 days postdose 3	1 day	Recovered	None
AN 57020	Fetal distress syndrome	257 days postdose 1	3 days	Recovered	None
AN 42260	Premature rupture of membrane Cervic dystocia	356 days postdose 2 356 days postdose 2	22 hours 2 days	Recovered Recovered	None None
AN 43892	Postpartum hemorrhage (moderate)	315 days postdose 3	2 days	Recovered	None

Source: From Table 8-18, CSR 015v2, p. 325-30

- The **SAEs in placebo recipients** were similar in nature to those seen in the Gardasil group. The SAEs seen in placebo recipients (excluding deaths) included threatened abortions (3), imminent abortion with premature labor (1), failed trial of labor (1), prolonged pregnancy (2), fetal distress syndrome (2), premature labor (2), premature rupture of membranes (1), CPD with failed trial of labor (2), CPD (3), breech presentation with premature labor (1), brow presentation with asphyxia (1), PID (2), ectopic pregnancy (1), cervical incompetence (1), vaginal laceration (1), preeclampsia (1), cervical hemorrhage uterine (1), cervix dystocia (1), pregnancy induced hypertension and UTI (1), UTI (1), urinary retention (1), pyelonephritis (1), gastritis (1), gastroenteritis (1), GI infection (1), abdominal pain (1), pneumonia (1), face edema (1), chemical poisonoing (1), hypersensitivity (1), uterine infection (1), thyroid cancer (which was likely present prior to vaccination by history) (1), allergic reactions (1), anaphylactic reaction (1), motor vehicle accident (1), aortic valve disease with hypertension (1), contact dermatitis (1), pain in extremity (1), chills with headache and fever (1), pneumomediastinum (1), and typhoid fever (1). (Source: From Table 8-18, CSR 015v2, p. 325-30)

Subjects who discontinued due to an Adverse Event

- 18 subjects discontinued due to an AE: 10 were in the vaccine group and 8 in the placebo group. This group included 5 in each group who died during the study (see deaths above for description).
- The other 5 subjects (all recovered) who discontinued from the study in the Gardasil group included the following:
  - **AN 42548** who developed **polyarthritis** of moderate intensity (later diagnosed as **carpal tunnel syndrome)** 20 days following dose 1
  - **AN 42899** who developed **injection site swelling and erythema** and 2 episodes of **dizziness** (lasting 2 hours [moderate], and 30 minutes [severe] at 1 day following dose 2
  - **AN 43424** who developed severe **urticaria** immediately following dose 1
  - **AN 55232** who developed **bronchial irritation** on the day of dose 1
  - **AN 57005** who developed a **rash** on her left forearm of moderate intensity with a duration of 3 days at 1 day following dose 1.
- The 3 **placebo recipients** (all recovered) discontinued for:
  - **Fever** 5 days following dose 1
  - **Influenza** on the day of dose 1 (lasting 38 days)
  - **Fever** 2 days following dose 2, then **eczema** 3 days later. (Source: Table 8-19, CSR 015v2, p. 332-333 and Section II.11.5.5, p. 1067-8)

Statsitical Comparison of Serious Adverse Events and Severe Injection Site Adverse Events

- The number and proportion of subjects with SAEs within 15 days after any vaccination were similar in the Gardasil group (N=17) and placebo group (N=16). Table 70 below presents these data and the statistical comparison.

TABLE 70
Protocol 015: Comparison of Vaccination Groups with Respect to the Number (%) of Subjects who Reported SAEs Days 1-15 days After any Vaccination or Vaccine Related SAEs at Any Time During the Study

	Gardasil N=6075	Placebo N=6076	Risk Difference (Gardasil – Placebo)	95% CI
Subjects with follow-up	6019	6031		
Number (%) with SAE after any vaccination visit	17 (0.3%)	16 (0.3%)	0.0	(-0.2, 0.2)
Number (%) with Vaccine Related SAEs at any time during the study	3 (0.0%)	2 (0.0%)	0.0	(-0.1, 0.1)

Source: Table 8-20, CSR 015v2, p. 335

- There was a slightly higher percentage of severe injection site reactions 1-5 days after any vaccination visit (2.2%) in the vaccine group as compared to the placebo group (0.9%) in the 5 days after any vaccination visit. (See Table 71 below).

TABLE 71
Protocol 015: Comparison of Vaccination Groups with Respect to the Number (%) of Subjects who Reported Severe Injection Site AEs Days 1-5 Days After Any Vaccination – Detailed Safety Cohort (US)

	Gardasil N=457	Placebo N=454	Risk Difference (Gardasil – Placebo)	95% CI
Subjects with follow-up	448	447		
Number (%) with SAE after any vaccination visit	10 (2.2%)	4 (0.9%)	1.3	(-0.3, 3.3)

Source: Table 8-21, CSR 015v2, p. 336

Pregnancy Outcomes

- During the course of the study, 1211 subjects became pregnant. At the time the database was closed, app. 76% of outcomes were known. Most of the pregnancies for whom the outcomes were not known were ongoing.

TABLE 72
Protocol 015: Pregnancy Outcome Summary
(Entire Study Period, All Vaccinated Subjects)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=6075)		Placebo (N=6076)	
	n	(%)	n	(%)
Number of subjects	6075		6076	
Subjects with pregnancies	575	(9.5)	636	(10.5)
Subjects without pregnancies	5500	(90.5)	5440	(89.5)
Number of pregnancies †	631		692	
Number of pregnancies with unknown outcome	155		165	
Number of fetuses/infants with known outcome	478		528	
Live Births‡	276	(57.7)	304	(57.6)
Method of Delivery				
C-Section §	53	(19.2)	68	(22.4)
Repeat or Elective Section	15	(5.4)	13	(4.3)
Fetal Distress	12	(4.3)	17	(5.6)
Failure to Progress or Dystocia	12	(4.3)	9	(3.0)
Cephalopelvic Disproportion	5	(1.8)	10	(3.3)
Breech, Malpresentation, or Transverse Lie	7	(2.5)	14	(4.6)
Cord Prolapse, Placenta Previa	0	(0.0)	0	(0.0)
Premature Delivery; Multiple Gestation	4	(1.4)	4	(1.3)
Other	7	(2.5)	16	(5.3)
Vaginal	223	(80.8)	235	(77.3)
Infant Outcome				
Normal	256	(92.8)	293	(96.4)
Abnormal	20	(7.2)	10	(3.3)
Congenital Anomaly	6	(2.2)	2	(0.7)
Other Medical Conditions	16	(5.8)	8	(2.6)
Unknown	0	(0.0)	1	(0.3)
Fetal Loss‡	202	(42.3)	224	(42.4)
Type of Loss				
Spontaneous Abortion	126	(62.4)	135	(60.3)
Late Fetal Death	8	(4.0)	6	(2.7)
Elective Abortion	68	(33.7)	83	(37.1)
Fetal Outcome				
Normal	9	(4.5)	8	(3.6)
Abnormal	3	(1.5)	11	(4.9)
Congenital Anomaly	0	(0.0)	2	(0.9)
Other Medical Conditions	3	(1.5)	7	(3.1)
Unknown	190	(94.1)	205	(91.5)

† A subject may have more than one pregnancy during the study. Each pregnancy is counted once. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually.
‡ Percentages of 'Live Births' and 'Fetal Loss' are calculated based on the number of fetuses/infants with known outcome. Percentages under 'Method of Delivery' and 'Infant Outcome' are calculated based on 'Live Births'. Percentages under 'Type of Loss' and 'Fetal Outcome' are calculated based on 'Fetal Loss'.
§ A subject may have more than one reason for C-section for a single pregnancy.
N = Number of subjects who received only the clinical material indicated in the given column.
Number of subjects: Number of subjects vaccinated in each vaccination group.
HPV = Human papillomavirus; VLP = Virus-like particles.

Source: Table 8-22, CSR 015v2, p. 339

- When the Latin American countries are excluded, there is a lower percentage of spontaneous abortions (fairly equal between the treatment groups), and a higher percentage of elective abortions. (Source: Table 8-23, CSR 015v2, p. 341, not shown here)
- Also, the rates of spontaneous abortions were calculated for the pregnancies whose outcomes are known (including those with and without subject in Latin America). As noted in Table 73 below, the rates of spontaneous abortions are very similar for the vaccine and placebo groups. The rates decrease if the subjects from Latin America are excluded.

TABLE 73
Protocol 015: Percentages of Subjects with Spontaneous Abortions (Including all Subjects with Known Outcomes, with or without Subjects from Latin America)

	All Subjects		Subjects excluding those from Latin America	
	Vaccine	Placebo	Vaccine	Placebo
Pregnancies with known outcome	478	528	261	273
Spontaneous abortions	126	135	56	53
Percentages of pregnancies with known outcomes with spontaneous abortions	26.3%	25.5%	21.4%	19.4%

Source: From Table 8-22 (p. 339) and Table 8-23 (p. 341), CSR 015v2

- The proportions of pregnancies resulting in fetal loss were comparable between the 2 groups. Among the 31 fetuses who underwent an assessment, 2 fetuses (both from the placebo group) were found to have a congenital anomaly.

Serious Adverse Events Reported During Pregnancy

- These were included in the SAE section.
- There were 24 vaccinees and 28 placebo recipients with SAEs during pregnancy, representing 4.2% and 4.4% of women who reported a pregnancy in each group.
- There was no apparent difference in the percentages of subjects with SAEs during pregnancy in the treatment groups. (Source: Table 11-174, CSR 015v2, p. 881-5, not shown here) (Narratives: p. 1048-1063)

Infant SAEs

- These SAEs are presented in tabular form and narratives in the BLA.
- A total of 38 infants born to 37 subjects in the vaccine group experienced an SAE. One baby was diagnosed with congenital megacolon.
- A total of 24 infants born to 24 subjects in the placebo group experienced an SAE. There were 2 additional subjects (AN 40330 and 46561) whose fetuses had a congenital anomaly and died in utero. These were not felt to be study material related by the investigator.
- SAEs in infants who were breastfeeding were reviewed.
  - There were 10 infants born to 8 women in the vaccine group, and 5 infants born to 5 women who were breastfeeding in the placebo group with an SAE. GI and respiratory illnesses were the majority of these events.
- Narratives of these infants were reviewed (p. 1068-84, CSR 015v2).
- Of the 478 infants whose outcomes were known in the Gardasil group, there were 276 live births. 38 babies born to 37 subjects had an SAE, and some of these included babies exposed to vaccine during breastfeeding (10 SAEs in 8 infants).
- Of the 528 infants whose outcomes were known in the placebo group, there were 304 live births. 24 babies from 24 pregnancies had an SAE, and some of these included babies who were exposed to vaccine during breastfeeding (6).
- One in each group of the infants exposed during breastfeeding were also exposed in utero.
- There was a higher percentage of abnormal outcomes in the vaccine group for live births (N= 20 or 7.2%) as compared to the placebo group (N=10 or 3.3%), although

there was a higher abnormal fetal outcome with fetal loss in the placebo group (N=11 or 4.9% in the placebo group as compared to N=3 or 1.5% in the vaccine group). (Source: Table 8022, CSR 015v2, p. 339, not shown here). The timing and nature of the abnormalities were reviewed.

Congenital anomalies (Note: Congenital anomalies in all studies are discussed in further detail in the Safety Summary section of this review.)

- 8 infants with congenital anomalies were identified in the **Gardasil** group. No consistent pattern of anomalies was identified.
  - 5/8 anomalies were noted in children conceived > 1 month from the time of vaccination.
    - 1 child with a branchial cyst exposed app. 6 months after dose 3
    - 1 child with a chromosomal translocation 9/15 app. 3 months after dose 3 (the father was reportedly a carrier for this abnormality, and the child was lost to follow-up)
    - 1 child with persistent fetal circulation who was conceived app. 4 months after dose 2
    - 1 child with a cardiac murmur conceived app. 1 year postdose 3
    - 1 child with an anomalous pulmonary venous circulation conceived app. 2 months after dose 2 (this child died with pneumonia, after also being exposed to the vaccine 21days postdose 3 via breastfeeding).
  - 3/8 anomalies were conceived within 1 month of vaccination in the mother.
    - 1 child with congenital megacolon who was conceived near the time of dose 3
    - 1 child with talipes equinovarus conceived near the time of dose 1
    - 1 child with trisomy 21, duodenal atresia, and congenital heart disease conceived app. 3-4 weeks after dose 1 (this child died). The congenital anomalies are discussed in further detail in the Safety Summary section of this review, but there is no consistent pattern of anomalies noted.
- 5 infants with congenital anomalies were identified in the **placebo group**, one who died in utero with multiple anomalies, and an additional sixth child died in utero.
  - All these children were conceived > 1 month after vaccination.
    - 1 child with VSD conceived app. 6 months postdose 3
    - 1 child with polydactyly conceived 1 year postdose 3
    - 1 child with congenital hip dysplasia app. 2-3 months postdose 3
    - 1 child with auricular agenesis
    - 1 child with multiple anomalies conceived > 1 year postdose 3.
    - The other child who died in utero was conceived app. 1 year postdose 3.
    - [There was one additional congenital anomaly submitted in a safety report to the IND. This child was born to a placebo recipient and was diagnosed with right auricular agenesis. All updates are noted in the overall safety summary.]

Prematurity

- There were 7 children in the **Gardasil** group who were born prematurely. 4 were conceived > 1 month after a vaccine dose (at 3, 3, 4 and > 12 months after a dose of vaccine in their mothers). 3 were conceived either around the time of vaccination (2 infants) and one app. 3-4 weeks after dose 3 (also with fetal growth retardation; this child died of bronchiolitis and sepsis).
- In the **placebo group**, there were 5 children who were born prematurely. Two were conceived > 1 month from the last vaccination (> 1 month [this child also had meningitis], 2 and ½ months, and > 1 year), and 2 were conceived within a month of vaccination (at time of vaccination and app. 1 month).

Small for gestational age, low birth weight

- There were 2 such infants in the **Gardasil** group, both conceived > 1 month after a vaccine dose (4 months postdose 3, and 1 year postdose 3).

Fetal distress:

- There was one infant in the **Gardasil** group conceived around the time of vaccination with this event, and the infant recovered (also had jaundice).

Respiratory distress

- In the **Gardasil** group, there were 3 such events. One child with asphyxia (who recovered) was conceived around the time of vaccination; and one child with dyspnea (recovered) was conceived app. 4 months postdose 2; and one child had meconium aspiration (conceived at the time of dose 1).
- In the **placebo** group, there were 2 such events: one child had respiratory distress and recovered was conceived approximately at the time of dose 1, and one with amniotic fluid aspiration and recovered was conceived approximately 1 month after dose 3.

- **Infections (Exposed in utero)**
  There were 5 infants in the **Gardasil** group with infections, including infective mastitis (conceived > 1 year following dose 3); one with pneumonia and the twin with bronchiolitis (conceived 1 year following dose 3); one with pneumonia (conceived 3-4 months following dose 3); and one with pneumonia (conceived 4-5 months following dose 3).
- In the **placebo** group, there were 4 infants with infections, including one with pneuomia (conceived at the time of dose 3); one with rotavirus gastroenteritis (conceived 5 months following dose 3); one with viral meningitis (conceived approximately 2 weeks following dose 3); and one with bronchiolitis X 2 and diarrhea (conceived 4-5 months following dose 3).

Infections (Exposed via breastfeeding)

- There were 7 infants in the **Gardasil** group. These included one with gastroenteritis at Day 38 following dose 2; one with an URI at Day 44 following dose 1 and gastroenteritis at Day 48 following dose 1; one with pneuomonia at Day 129 following dose 2; one with bronchopneumonia at Day 12 following dose 1; one with pneumonia

at Day 29 following dose 1; one with diarrhea at day 126 following dose 3; and one with pneumonia and asthma at days 20 and 24 following dose 2.

- In the **placebo** group there were 4 subjects, including one with gastroenteritis at Day 16 following dose 3; one with bronchiolitis (also with prematurity) at Day 25 following dose 3; one with pneumonia at Day 135 following dose 2; and one with gastroenteritis a Day 107 following dose 2.
- It is difficult to ascribe causality because these events are commonly seen in this age group, and in this study occurred at variable times in relation to vaccination. Similar events are seen in the both treatment groups. See overall safety conclusion.

Deaths due to unknown causes or SIDS after birth

- Two children in the **Gardasil** group fell into this group: one child died of SIDS (had been conceived approximately 1 month following dose 3). One child died approximately at 2 months of age (conceived approximately 6 months after the last dose of vaccine). No diagnosis was able to be obtained for this infant.
- There were no SIDS deaths from the placebo group.

Other Infant AEs

- In the **Gardasil** group, 1 child had malnutrition (conceived 3-4 months following dose 2); 1 child had dehydration at day 20 following dose 3 of breastfeeding; 1 child had a clavicle fracture due to vaginal birth (conceived at the time of dose 3); 1 had a head injury at 23 days following dose 3 of breastfeeding.
- In the **placebo** group, 1 child had a febrile seizure 36 days after dose 3 of breastfeeding; 1 child had hypoglycemia (conceived at the time of dose 3); 1 child had asthma at 46 days after dose 1 of breastfeeding; 1 child had GE reflux (conceived approximately 1 month following dose 3)

TABLE 74
Protocol 015: Infants (live births) with SAE Born to Mothers who Received Gardasil or Placebo

Condition	Gardasil	Placebo
Congenital anomalies	8	5
Prematurity	7	5
Small for gestational age, low birth weight	2	0
Fetal Distress	1	0
Respiratory distress	3	2
Jaundice	2	2
Infections (exposed in utero)	5	4
Infections (exposed via breastfeeding)	7	4
Deaths due to unknown cause or SIDS	2	0
Others	4	3

Source: From Table 8-25, CSR 015v2, p.346-50 and narratives

- In summary, there were a somewhat higher number of infants with an SAE in the vaccine group as compared to the placebo group, and were without clear association to study material administration.

Reviewer's Comment: Although infant SAE reports were slightly higher among Gardasil recipients, there was no clear pattern or causal association noted that would generate additional safety concerns. Please see integrated safety summary for more information.

New Medical History

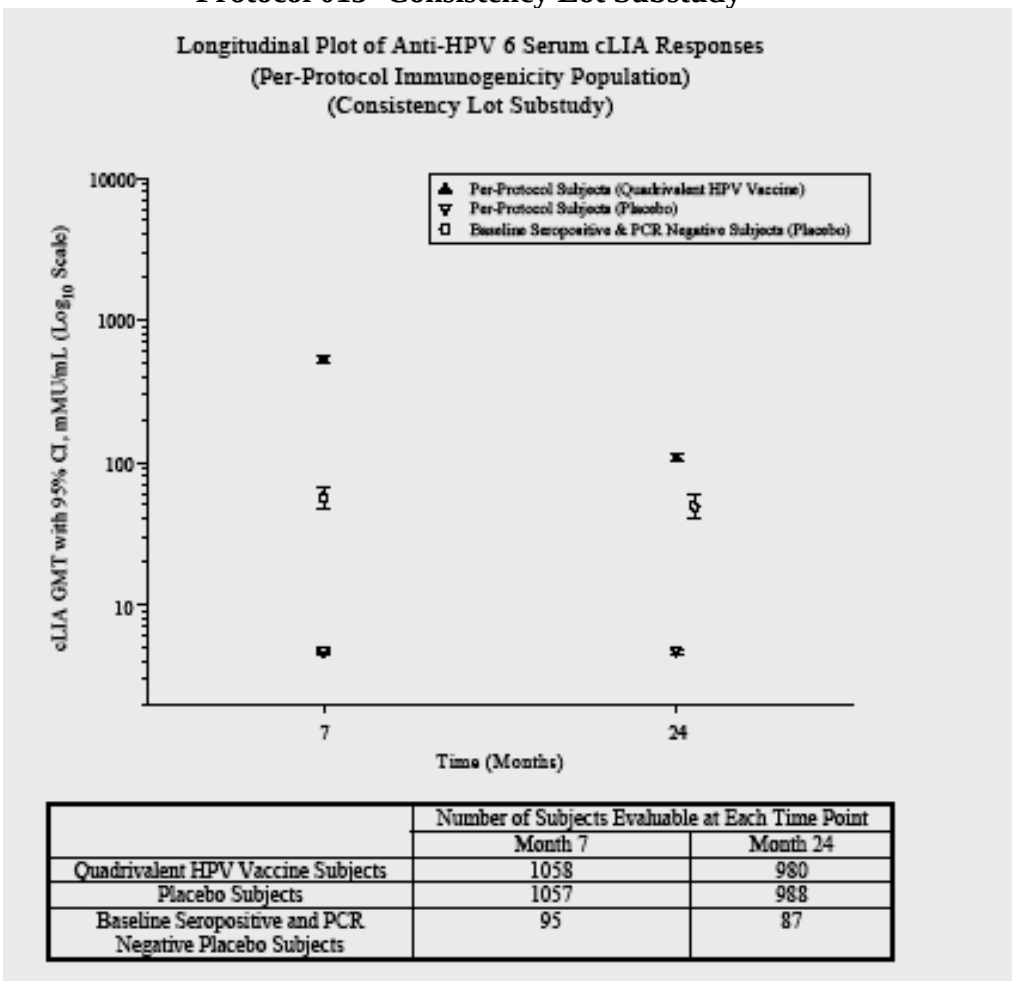
- In the **Detailed Safety Cohort**, the most common new medical condition reported during Day 1 to Month 7 was infection (mostly URIs). The proportions of subjects who reported new medical conditions were generally comparable between the two groups.
- In the follow-up period, the most commonly reported new medical conditions were infections followed by surgical/medical procedures. The proportions of subjects who reported new medical conditions were generally comparable between the 2 groups. (Sources: Tables 8-27 and 8-28, CSR 015v2, p. 353-6, not shown here).

Immunogenicity Results

Exploratory Analyses of Persistence of Immune Responses

- Postvaccination data were collected at Month 7 and Month 24 from subjects participating in the Consistency Lot substudy. The primary analysis was conducted in the PPI population (like the PPE population, with day ranges given for vaccination and serum collection).
- At Month 7 and Month 24, the point estimates of the percent who were seropositive and PCR negative for all types was $\geq$ 95%, except at for HPV 18 at Month 24, where the percent seropositive was 68.2% (95% CI 65.3%, 71%). The clinical significance of this finding was not clear, since no breakthrough HPV 18 related disease cases were reported in any of the prophylactic efficacy analyses.
- The type specific GMTs declined from Month 7 to Month 24. These are shown in the following figures (9-12) for each of the vaccine HPV types.

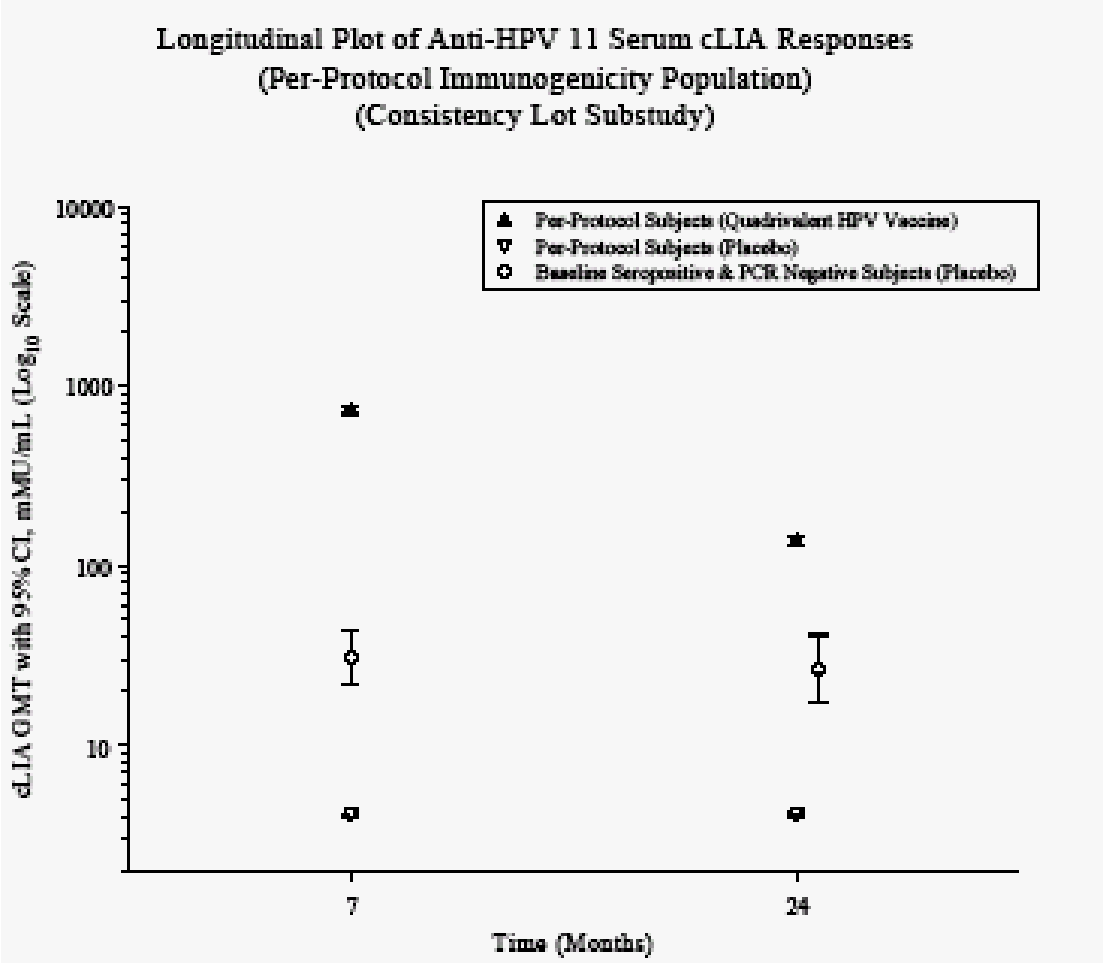
FIGURE 9
Protocol 015 -Consistency Lot Substudy



	Number of Subjects Evaluable at Each Time Point	
	Month 7	Month 24
Quadrivalent HPV Vaccine Subjects	1058	980
Placebo Subjects	1057	988
Baseline Seropositive and PCR Negative Placebo Subjects	95	87

Source: Figure 11-8, CSR 015v2, p. 679

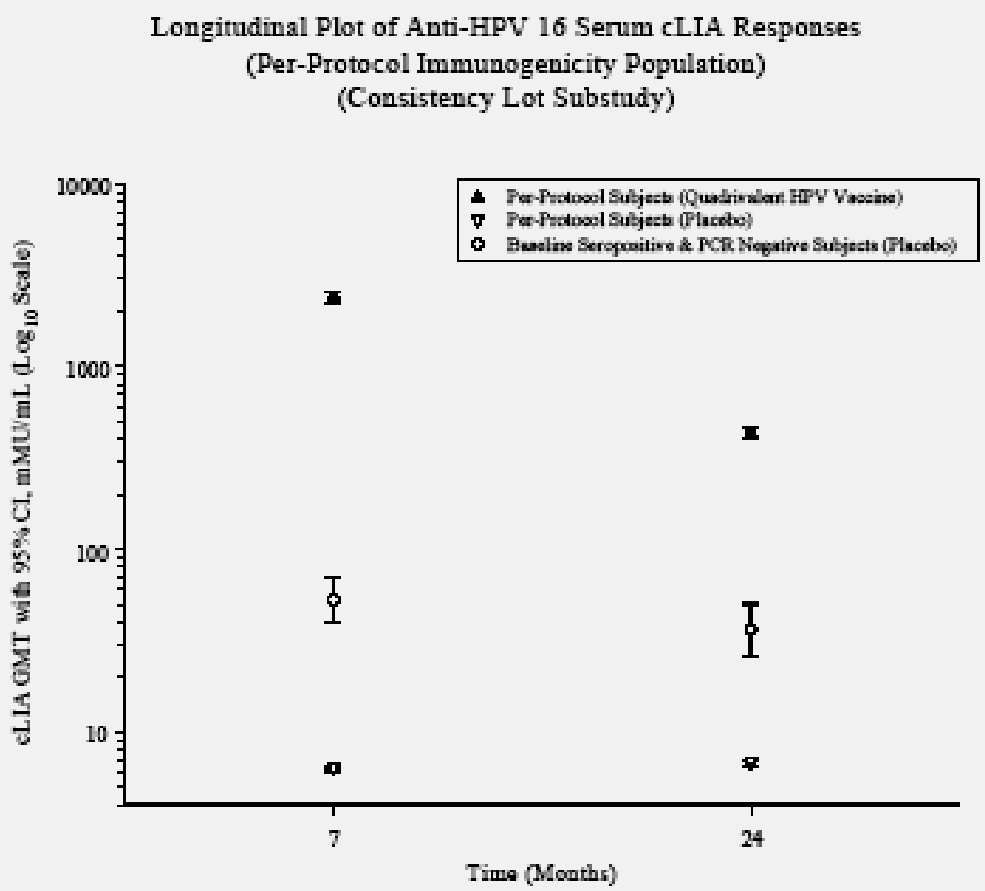
FIGURE 10
Protocol 015 – Consistency Lot Substudy



	Number of Subjects Evaluable at Each Time Point	
	Month 7	Month 24
Quadrivalent HPV Vaccine Subjects	1058	980
Placebo Subjects	1057	988
Baseline Seropositive and PCR Negative Placebo Subjects	21	20

Source: Figure 11-9, CSR 015v2, p. 680

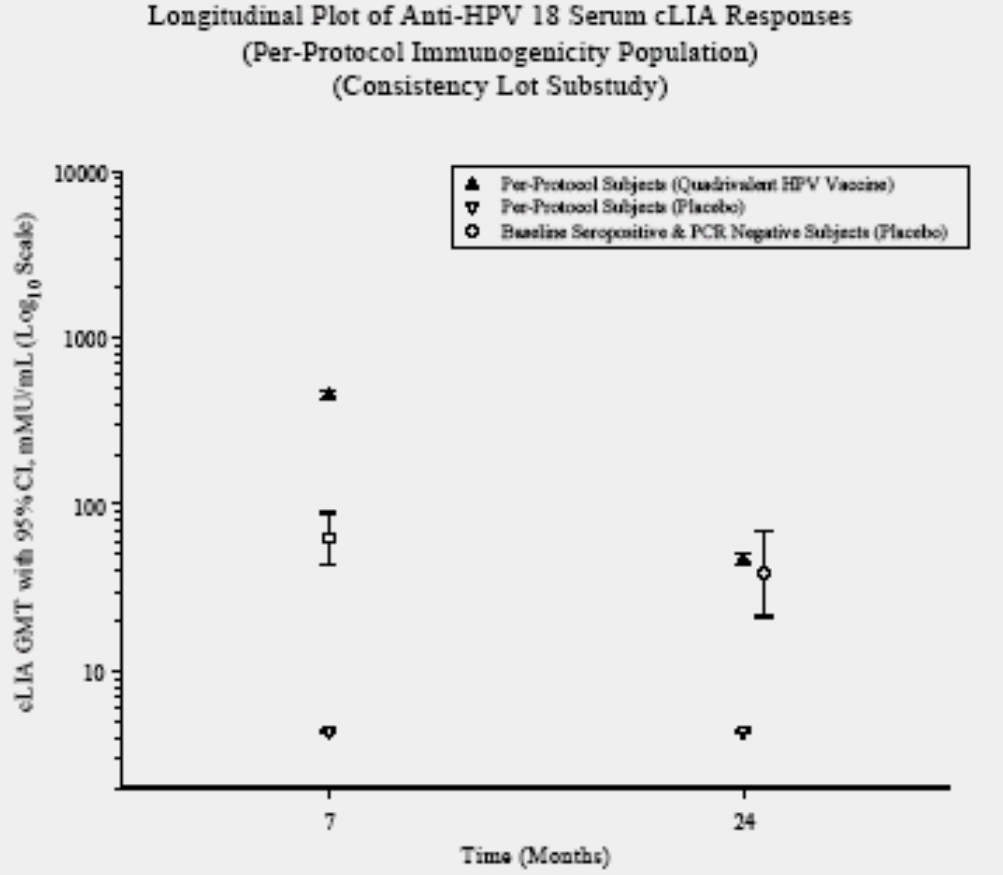
FIGURE 11
Protocol 015 – Consistency Lot Substudy



	Number of Subjects Evaluable at Each Time Point	
	Month 7	Month 24
Quadrivalent HPV Vaccine Subjects	995	927
Placebo Subjects	1016	953
Baseline Seropositive and PCR Negative Placebo Subjects	102	96

Source: Figure 11-10, CSR 015v2, p. 681

FIGURE 12
Protocol 015 – Consistency Lot Substudy



	Number of Subjects Evaluable at Each Time Point	
	Month 7	Month 24
Quadrivalent HPV Vaccine Subjects	1119	1043
Placebo Subjects	1140	1060
Baseline Seropositive and PCR Negative Placebo Subjects	42	34

Source: Figure 11-11, CSR 015v2, p. 682

Reviewer's Comment: Anti-HPV 16, 11, and 6 remain higher at Month 24 compared to placebo subjects who were initially seropositive and PCR negative at baseline. The GMT of anti-HPV 18 at Month 24 in vaccine recipients was 47.6 mMU/mL [95% CI: 43.7, 51.8] who were initially seronegative and PCR negative for HPV 18 at baseline. In subjects who received placebo and were seropositive and PCR negative at baseline for HPV 18, the Month 24 anti-HPV 18 GMT was 38.7 mMU/mL [95% CI: 37.5, 128.1]. (See Table 75 below.)

TABLE 75
Protocol 015 Month 24 (Consistency Lot Substudy):
Anti-HPV cLIA GMTs by Day 1 Serostatus and PCR Status

	Cohort	Gardasil N=1512		Placebo N=1511	
HPV Type	Serostatus and PCR Status	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	Sero (-), PCR (-)	1054	108.9 (102.6, 115.5)	1073	<8 (<8. <8)
	Sero (+), PCR (-)	76	429.8 (331.7, 556.9)	87	49.4 (40/4, 60.4)
	Sero (+), PCR (+)	27	398.8 (277.2, 573.9)	27	65.3 (41.2, 103.4)
HPV 11	Sero (-), PCR (-)	1054	138.5 (130.3, 147.2)	1073	< 8 (<8, <8)
	Sero (+), PCR (-)	18	716.5 (396.7, 1294.0)	20	26.7 (17.3, 41.2)
	Sero (+), PCR (+)	1	77.0 (N/A)	1	< 8 (N/A)
HPV 16	Sero (-), PCR (-)	1024	442.6 (414.8, 472.3)	1025	< 12 (<12, <12)
	Sero (+), PCR (-)	66	786.7 (601.5, 1029.0)	96	36.4 (26.4, 50.2)
	Sero (+), PCR (+)	63	1035.7 (790.5, 1356.9)	57	70.5 (47.0, 105.6)
HPV 18	Sero (-), PCR (-)	1123	47.6 (43.7, 51.8)	1144	<8 (<8, <8)
	Sero (+), PCR (-)	43	336.7 (226.4, 500.8)	34	38.7 (21.4, 70.1)
	Sero (+), PCR (+)	8	212.1 (93.0, 483.6)	20	69.3 (37.5, 128.1)

N=Number of subjects in Consistency Lot Substudy randomized to the respective vaccination group with at least one injection.
n = Number of evaluable subjects in cohort
(Source: Protocol 015v2, Table 7-24, p. 279)

- Also shown are the actual GMTs for each vaccine HPV type at Month 7 and Month 24. The GMTs for all vaccine HPV types are highest at Month 7 (app. 528 mMU/mL, 733 mMU/mL, 2388 mMU/mL and 452 mMU/mL for anti-HPV 6, 11, 16 and 18, respectively), and decrease at Month 24.
- However, the lowest GMTs are usually higher than those seen in subjects who received placebo and had evidence of previous infections. (Source: Table 7-22, CSR 015v2, p. 275, not shown here)

Impact of Vaccination on antibody levels in those who were initially seropositive

- In general, subjects who were seropositive to the relevant HPV type at baseline had higher GMTs at Month 7 and Month 24 than those who were initially seronegative. (Source: Tables 7-23 and 7024, CSR 015v2, p. 278-9, not shown here)

Reviewer's Comment: In general, baseline seropositivity appeared to have a greater impact on immune response to Gardasil than did baseline PCR positivity status.

Consistency Lot Substudy (Substudy of Protocol 015)
The hypotheses for the substudy were as follows:

- **Primary Immunogenicity Hypothesis:** Three separate lots of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induce similar immune responses, as measured by the serum cLIA geometric mean titers (GMTs) to HPV 6, 11, 16, and 18, at Week 4 Following dose 3. [Each vaccine component was to be analyzed separately. The statistical criterion for consistency required that the upper bound of the confidence interval for the fold difference in GMTs between any 2 lots exclude a fold-difference of 2 or greater for each HPV type.]
- **Secondary Immunogenicity Hypothesis:** Three separate lots of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induce similar immune responses, as measured

by the percentages of subjects who seroconvert (i.e., change serostatus from seronegative to seropositive) for each of HPV Types 6, 11, 16, and 18 by Week 4 Following dose 3. The cut-offs for anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.]

[Each vaccine component was to be analyzed separately. The statistical criterion for similarity requires that the upper bound of the confidence interval for the maximum absolute difference in proportions between any 2 of the 3 lots exclude 5 percentage points or more for each HPV type.]

Study design

- 1500 subjects were randomized in a 1:1:1 ratio to receive one of the three consistency lots, and 1500 were randomized to receive placebo.
- Subjects were enrolled toward the end of enrollment for the efficacy study. At the time 8500 subjects were enrolled in the CIN 2/3 efficacy study, 3000 subjects were enrolled in the consistency lot substudy in a ratio 1:1:1:3 to receive 1 of 3 lots of vaccine or placebo.
- Some subjects in the US and Puerto Rico were dually enrolled in the NSAE substudy and the consistency lot substudy.
- For subjects in the Consistency Lot substudy, blood samples were obtained for anti-HPV serology testing at baseline (Day 1) and Month 7 using (cLIA) assay for HPV 6, 11, 16, and 18 responses.
- Other procedures were as in the Protocol 015.

Statistical Considerations:

Analysis Populations (These were defined earlier in the review.)

- **Per Protocol** population (primary approach)
- **All type-specific HPV-naïve subjects with serology data** population

Immunogenicity Analysis Methods

- The evaluation of similarity in GMTs among lots was based on 3 pairwise comparisons for each vaccine HPV type for the primary immunogenicity endpoints.
- For each HPV type, an analysis of variance (ANOVA) model was to be constructed with natural log titer as the dependent variable and treatment group, study center, and treatment-by-study center interaction as fixed effects.
- All 3 lots would be considered consistent with respect to GMTs for a given vaccine HPV type if all 6 one-sided p-values for that vaccine HPV type were <0.05, or, equivalently, if all 3 pairwise 90% two-sided confidence intervals of the GMT ratio for the vaccine HPV type were entirely within (0.5, 2). (Please see statistical review by Dr. Henry Hsu.)

Data Analysis

- The primary time point for the immunogenicity analysis for the Consistency Lot substudy was Month 7.
- The immunogenicity analysis was conducted when all subjects in the substudy completed the Month 7 follow-up.

Changes in Statistical Analyses: See Appendix 7 for changes in statistical analysis for Consistency Lot substudy.

Accounting of Subjects in Substudy

- A total of 1514 subjects were enrolled in the Consistency Lot Substudy.
  - Of the 1514 subjects randomized, 2 were not vaccinated.
  - Of the 1514 subjects randomized, 96.8% completed the 3 dose vaccination period (through Month 7).
  - The number of subjects who discontinued was generally comparable among the 3 groups. The most common reason for discontinuation was consent withdrawal. The proportions of subjects who discontinued the study and distributions were generally comparable among the 3 groups.
  - 500 subjects randomized into Group 1, 510 into Group 2, and 504 into Group 3.

Demographics

- Mean age: overall was 20.3 years.
- Ethnic groups: White (66.1%), with 15.9% Hispanic, 4.2% black, 4% Asian, and 9.8% other.

Summary Results of anti-HPV Serum cLIA Data (See Statistical Review by Dr. Henry Hsu for full analysis)

- For each HPV type, the Month 7 GMTs were generally comparable among the 3 consistency lots in both populations.
- Regarding seroconversion, almost all subjects seroconverted for each vaccine HPV type.
- For consistency lot 1, there were 2 subjects in the vaccine group who did not seroconvert, and on the day they were seen in the same clinic, 2 placebo subjects did seroconvert. This occurred on 10/21/03 at study site 015-057.
- Similar findings were seen for 2 subjects (one Consistency lot 3 and one placebo) seen at study site 015-030, and had sera drawn on 10/22/03.
- There was one other vaccine recipient who did not seroconvert and one placebo recipient who did seroconvert at Month 7 at site 015-040, but one was seen 9/6/03 and one was seen 10/18/03. It is known that all these subjects received the correct study material, and the sponsor notes that it was possible that the serology samples may have been inadvertently switched.

TABLE 76
Protocol 015: Summary of Anti-HPV Serum cLIA GMTs by Consistency Lot and Seroconversion Rates (Per Protocol Population)

Assay (cLIA)	Time Point	Cons Lot 1 N=499			Cons Lot 2 N=509			Cons Lot 3 N=504		
		n	GMT mMU/mL (95% CI)	Seroconversion (95% CI)	n	GMT (95% CI)	Seroconversion (95% CI)	n	GMT (95% CI)	Seroconversion (95% CI)
Anti-HPV 6	Month 7	349	523.7 (481.1, 569.9)	348/349 99.7% (98.4, 100%)	364	567.3 (525.3, 612.6)	364/364 100% (99, 100%)	343	491.9 (451.6, 535.8)	342/343 99.7% (98.4, 100%)
Anti-HPV 11	Month 7	349	709.7 (646.5, 779.2)	348/349 99.7% (98.4, 100%)	364	759.6 (695.8, 829.3)	364/364 100% (99, 100%)	343	728.7 (660.6, 803.7)	341/343 99.4% (97.8, 99.9%)
Anti-HPV 16	Month 7	326	2395.8 (2087.7 2749.3)	325/326 99.7% (98.3, 100%)	356	2692.2 (2394.7, 3026.7)	356/356 100% (99, 100%)	333	2092.4 (1824.5, 2399.8)	331/33 99.4% (97.8, 99.9%)
Anti-HPV 18	Month 7	367	429.7 (386.2, 478.1)	364/367 99.2% (97.6, 99.8%)	392	487.1 (441.4, 537.5	391/392 99.7% (98.6, 200%)	380	438.7 (394.5, 487.8)	377/380 99.2% (97.7, 99.8%)

N=Number of subjects randomized to respective vaccination group who received at least 1 injection;
n= Number of subjects contributing to analysis
Seroconversion = change in status from seronegative to seropositive. Seropositivity was defined as anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Tables 7-1 and 7-2, CSR 015v1, p. 114-115

- The Reverse Cumulative distributions for all 4 vaccine HPV types for the 3 consistency lots are very similar. (Source: Figures 7-1, 7-2, 7-3, 7-4, CSR 015v1, p. 116-9, not shown here)
- For each comparison, the lower bound of the 90% confidence interval of GMT ratio between the comparison lots was greater than 0.5 and the upper bound was less than 2.0. Therefore, equivalence was shown in all 3 pairwise comparisons for each vaccine HPV type. The sponsor indicated that they used the methodology as in Wiens, Heyse, and Matthews to demonstrate consistency of lots. The per protocol analysis results are shown in Table 77.
- Overall, for all HPV vaccine types, the Month 7 anti-HPV GMT responses from the 3 vaccine manufacturing lots met the pre-specified statistical criteria. This was shown for the per-protocol population and the all HPV naïve with serology population. (Source: Table 11-11, CSR 015v1, p. 175-6, not shown here)
- For all HPV types and pairs of lots, the treatment by region interaction was not significant ($p > 0.1$).
- CBER also requested that the sponsor provide 95% CIs for the ratio of GMTs. This additional analysis was considered to be exploratory by the sponsor, and they considered the first pre-specified analysis as the primary analysis. Please see statistical review by Dr. Henry Hsu for full analysis.

TABLE 77
Protocol 015: Statistical Analysis of Equivalence of GMTs at Month 7 Comparing Vaccine lots 1, 2, and 3 (PPI)

		Gardasil						Estimated Fold Difference Group A/Group B 90% CI	p-value for Equivalence
		Comparison Group A			Comparison Group B				Left, Right
Assay (cLIA)	Comparison Group A vs. Comparison Group B	N	n	Estimated GMT mMU/mL	N	n	Estimated GMT mMU/mL		
Anti-HPV 6	Lot 1 vs. Lot 2	499	349	554.8	509	364	602.3	0.92 (0.79, 1.07)	<0.001, <0.001
	Lot 1 vs. Lot 3	499	349	554.8	504	343	496.3	1.12 (0.96, 1.31)	<0.001, <0.001
	Lot 2 vs. Lot 3	509	364	602.3	504	343	496.3	1.21 (1.04, 1.42)	<0.001, <0.001
Anti-HPV 11	Lot 1 vs. Lot 2	499	349	737.7	509	364	807.3	0.91 (0.77, 1.08)	<0.001, <0.001
	Lot 1 vs. Lot 3	499	349	737.7	504	343	744.1	0.99 (0.83, 1.18)	<0.001, <0.001
	Lot 2 vs. Lot 3	509	364	807.3	504	343	744.1	1.08 (0.91, 1.29)	<0.001, <0.001
Anti-HPV 16	Lot 1 vs. Lot 2	499	326	2414.7	509	356	2932.4	0.82 (0.64, 1.06)	0.001, <0.001
	Lot 1 vs. Lot 3	499	326	2414.7	504	333	1932.2	1.25 (0.96, 1.62)	<0.001, 0.002
	Lot 2 vs. Lot 3	509	356	2932.4	504	333	1932.2	1.52 (1.18, 1.95)	<0.001, 0.035
Anti-HPV 18	Lot 1 vs. Lot 2	499	367	480.9	509	392	519.3	0.93 (0.76, 1.13)	<0.001, <0.001
	Lot 1 vs. Lot 3	499	367	480.9	504	380	452.4	1.06 (0.87, 1.30)	<0.001, <0.001
	Lot 2 vs. Lot 3	509	392	519.3	504	380	452.4	1.15 (0.94, 1.40)	<0.001, <0.001

N=number of subjects randomized to the respective group who received at least 1 injection.
n=number of subjects contributing to analysis
Source: From Table 7-3, CSR 015v1, p. 122-3

- The secondary immunogenicity hypothesis for the Consistency Lot substudy stated that 3 separate lots of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine would induce similar immune responses, as measured by the percentage of subjects who achieved seroconversion for HPV Types 6, 11, 16, and 18, by Week 4 Postdose 3. In both the PPI and all HPV naïve with serology populations (Source: Table 11-12, CSR 015v1, 177-8, not shown here), the pre-specified statistical criteria were met in all 3 pairwise comparisons for each vaccine HPV type.
- Overall, results in this section showed that for all vaccine components, the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine from 3 FMP consistency lots induced consistent type-specific Month 7 anti-HPV cLIA responses.
- The sponsor presented the safety data for this substudy. However, these safety data are part of the overall study results for Protocol 015 and are not presented in this section.

Comments-Conclusion Regarding Data for Protocol 015 (Reviewer's Opinion)
Conclusion:
Efficacy study: Results of Study 015 demonstrated efficacy for the quadrivalent HPV vaccine's efficacy in the prevention of HPV 16/18 related CIN 2/3 or worse in women 16-26 years of age who were naïve to the relevant HPV type. In the per protocol efficacy population, the VE was 100% [95% CI: 75.8, 100%]. It is noted that there were no cases of cervical cancer in either the vaccine or placebo group in Study 015 (or in the entire clinical development program).

For the modified intent to treat populations, the VEs were as noted below:
MITT Analyses (for HPV types 16/18 CIN 2 or worse):
MITT-1 population (like PPE population with protocol violators): VE = 100 % [95% CI: 82.6%, 100%].
MITT-2 population: (naïve to relevant HPV type, but efficacy assessed starting 30 days after 1 dose): VE = 97.2% [95% CI: 83.4%, 99.9%].
MITT-3 population: efficacy assessed starting 30 days after 1 dose: VE = 39.2% [95% CI: 16.9%, 55.8%]

Regional VE's: There were no cases in the per protocol efficacy population in the vaccine or placebo groups in Asia, which may have been due to the small number of subjects.

The vaccine is efficacious for those who are naïve (seronegative and PCR negative) for a specific vaccine HPV type. In subjects who PCR positive and/or seropositive with a vaccine type HPV, efficacy for the HPV type with which the subject was previously exposed and/or infected with was not demonstrated in exploratory analyses. (See further discussion below).

The MITT-1 and MITT-2 populations are like the PPE population in that naive subjects are assessed for efficacy against a specific vaccine HPV type. In a subject naïve to HPV 16, the vaccine appears effective in the prevention HPV-16 related CIN 2/3. However, that same subject may not be naïve to HPV 18 disease or non-vaccine HPV type, and

may develop a case of HPV 18 related disease or disease not related to one of the vaccine HPV types.

The MITT-3 population includes all subjects who received at least one vaccination, and were analyzed for efficacy, regardless of baseline vaccine type HPV status. As can be seen above, the efficacy against HPV 16/18 related CIN 2/3 was lower than that seen in the PPE (VE = 39.2% [95% CI: 16.9, 55.8%]).

Other Analyses:
VE against HPV 6, 11, 16, 18 related CIN: VE was 90.7% [95% CI: 74.4%, 97.6%]. The 4 cases that occurred in the vaccine group were HPV 16 related CIN 1 cases. One subject developed the abnormality at Month 7 (1 month after the 3rd dose); one subject may have had previous HPV 16 infection (she had a higher than normal anti-HPV 16 antibody level as compared to the PPI group in the Consistency Lot study, perhaps indicating an anamnestic response); one subject may have already been previously infected with HPV 16 (she had an anti-HPV 16 level of 18 mMU/mL at Day 1, so was technically seronegative, but may have really been infected); and the fourth subject had a lower than normal anti-HPV 16 level at Month 7 (as compared to the PPI Month 7 levels in the Consistency Lot substudy). The VE in the MITT-3 population was 46.6% [95% CI: 31.8, 58.4%].

VE against HPV 6, 11, 16, 18 EGL: VE was 98.6% [95% CI: 91.8%, 100%] in the PPE. There was one case of HPV 6 related EGL which was noted at Month 9, and this subject had a lower than normal anti-HPV 6 antibody level at Month 7 (again compared to the PPI population). In the MITT-3 population, the VE was 71.0% [95% CI: 58.8, 79.9%]. The efficacy against EGLs was higher in the MITT-3 population as compared to the efficacy against CIN, in part likely due to a lower rate of prevalent disease.

VE against HPV 6, 11, 16, 18 related CV and EGL: VE was 95.3% [95% CI: 88.6%, 98.5%] in the PPE. In the MITT-3 population, the VE was 55.4% [95% CI: 45.3, 63.7%].

VE against ALL CV and EGL:
VE against ALL CIN (due to any HPV type): This analysis was conducted in the restricted MITT-2 population (Pap had to be normal at Day 1 and naïve to all 4 vaccine types.) This population was interpreted as being a naïve population although a negative Pap does not rule out HPV related disease because of a sensitivity of approximately 70-85%. The sponsor was not able to provide the non-vaccine HPV types at the time the CSR was submitted. The VE was 19.8% [95% CI: <0, 38%]. In the MITT-3 population, the VE was 10.9% [95% CI: <0.0, 22.6%].

VE against ALL EGL: This analysis was also conducted in the restricted MITT-2 population. VE was 77.8% [95% CI: 64.1, 86.9%]. In the MITT-3 population, the VE was 47.6% [95% CI: 29.8, 58.0%].

Disease due to Vaccine versus Non-Vaccine HPV types: As noted above, the sponsor was not able to provide non-vaccine HPV type data, by HPV type, at the time of the CSR submission. This will be an important issue to follow. See comments for Protocol 005 (monovalent HPV 16 L1 VLP vaccine), as well as comments at end of document with overall assessment of efficacy, regarding this issue. It is likely that this issue will be addressed over time after the vaccine has been in use for a time. As per the sponsor, data are expected to be submitted in 2007 regarding the non-vaccine HPV types from this study. However, the sponsor did provide data on disease due to non-vaccine HPV types in sum (total disease minus disease due to vaccine HPV types) in this protocol. There were slightly more cases of non-vaccine HPV related CIN and EGL in the vaccine group as compared to the placebo group in the RMITT-2 population.

Impact on Pap tests: There was a slight decrease in most categories of Pap abnormalities in the vaccine group as compared to the placebo group.

Impact on gynecological procedures: Overall, there was a 21% reduction in gynecological procedures in the vaccine group [95% CI: 7.9, 32.3%] in the RMITT-2 population. There was a greater reduction in EGL biopsies in the vaccine group [54.7%; 95% CI: 37.3, 67.7%] compared to cervical procedures in the vaccine group [13.1%; 95% CI: <0, 26.4%].

Efficacy in subjects who are non-naïve (seropositive <u>and/or</u> PCR positive at Day 1) for CIN: These exploratory analyses were conducted on a subset of subjects, i.e., those non-naïve to a vaccine HPV type. The VE for vaccine HPV type related CIN 2 or worse was 17.8% [95% CI: <0.0, 41.3%]. (Source: Amendment 0019, Table 1e-3, Additional Efficacy Analyses Requested by CBER, p. 14, response 4/7/06). Interpretation of subgroup analyses are difficult, e.g., because these groups may not be well balanced.

- In subjects who were **seronegative and HPV PCR positive** for the relevant HPV type (possibly including recent infection), there was a lower rate of CIN 2 or worse in the vaccine group (27.4% decrease [95% CI: <0, 58.6%]), but again did not reach statistical significance.
- The efficacy for vaccine HPV type related CIN 2 or worse in those who are **seropositive and PCR negative** is 100% [95% CI: <0.0, 100%], but the case numbers are very low (3 in the placebo group versus 0 in the vaccine group).
- In those subjects who were **seropositive and PCR positive** for a vaccine HPV type, the vaccine efficacy for vaccine HPV type related CIN 2 or worse was 5.4% [95% CI: <0.0, 39.0%], with a case split of 41 in the placebo group [incidence rate of 6.3 per 100 person years at risk] and 42 in the Gardasil group [incidence rate of 6.0 per 100 person years at risk). (Source: Amendment 0019, p. 2, Table 1a-1, Additional Efficacy Analyses requested by CBER, response 4/7/06). (Please see Study 013 for findings in seropositive and PCR positive subgroup, as well as the overall efficacy section for further discussion.) Interpretation of subgroup analyses are difficult, e.g., because these groups may not be well balanced.

Efficacy in subjects who are non-naïve (seropositive <u>and/or</u> PCR positive at Day 1) for EGL: Similar exploratory analyses were conducted to assess the incidence of HPV 6,

11, 16, 18 related EGLs in subjects who were seropositive and/or PCR positive for the relevant vaccine HPV type. The findings were similar to those seen in subjects seropositive and PCR negative for CIN lesions above, in that there was a point estimate of 100% without statistical significance (and very few cases noted.) In the other subgroups, there was no evidence of efficacy of Gardasil against vaccine HPV type EGLs for the relevant HPV type with which they were infected prior to vaccination.

Immunogenicity:

Persistence: Antibody levels out to 24 months were reported. At Month 7 and Month 24, the point estimates of the seropositivity rates for HPV types 6, 11, and 16 types were $\geq$ 95%, and the seropositivity rate for HPV 18 at Month 24 was 68% [95% CI: 65.3, 71%]. The significance of this latter value is not clear, since no breakthrough cases related to HPV 18 were noted. Antibody levels at time points post-dose Month 24 were not yet submitted to the BLA for review.

- For all vaccine HPV types, GMTs at Month 24 were generally above the levels seen in subjects who were initially seropositive, (although the anti-HPV 18 antibody levels in vaccinees were only marginally higher.)
- In subjects who were initially seropositive and received vaccine, higher antibody levels were noted at Month 7 and Month 24 compared to subjects who were initially seronegative and received vaccine.
- No correlate of protection was identified.

In the **Consistency Lot Substudy**, 3 lots of FMP vaccine were found to be equivalent when comparisons of GMC ratios and differences in seroconversion rates were compared.

Safety:

SAEs were collected for all subjects, but AEs were collected by VRC's only in the NSAE substudy (N=911).

In the **NSAE substudy**, the following were noted:

- A slightly higher proportion of vaccinees experienced one or more AE compared with placebo recipients (91.3% vs. 88.4%, respectively).
- A slightly higher proportion of vaccinees experienced injection site AEs compared with placebo recipients (84.6% vs. 78.1%, respectively).
- A similar proportion of vaccinees and placebo recipients experienced a systemic AE (60.5% vs. 59.5%, respectively).
- Comparing dose 1, dose 2 and dose 3, there were a higher proportion of subjects experiencing a systemic AE after dose 1 compared to dose 2 or dose 3. There were a lower proportion of subjects with injection site AEs after doses 2 and 3 (app. 48%) in the placebo group compared to vaccinees (app. 60-63%).
- There was no evidence of increased reactogenicity in subjects who had evidence of previous vaccine type HPV exposure as compared to the naïve population in those who received the vaccine (and perhaps the rates were slightly lower in those previously exposed as compared to the naïve group). Most AEs were mild to moderate in intensity.

Regarding Injection site AEs Days 1-5 after any vaccination: There was a statistically significantly higher proportion of subjects with pain in the vaccine group as compared to the placebo group.

Regarding systemic AEs, there were no apparent risk differences between vaccinees and placebo recipients in the 15 days after any vaccination for specific systemic AEs. The most common systemic AEs were headache, nasopharyngitis, nausea, throat pain, upper abdominal pain, dysmenorrheal, pyrexia, diarrhea, fatigue and back pain (comparable proportions in the vaccine and placebo groups). There were a higher proportion of subjects in both groups with systemic AEs after Dose 1 compared with Dose 2 or Dose 3. Most systemic AEs in both groups were mild to moderate in intensity.
One systemic AE of interest in the General Safety Group was a subject with polyarthritis at Day 21 postdose 1 which was reported as a NSAE, but was described as continuing. However, this subject was diagnosed as having carpal tunnel syndrome.

Regarding Temperatures: Approximately 3% of subjects in each group had an elevated temperature (100 deg F – 102 deg F, oral), between Days 1-5 after any vaccination. There was no statistical difference between the two groups. There was no apparent difference after dose 1, 2, or 3, and no difference between those who were initially seropositive as compared to those who were initially seronegative.

Deaths: These are summarized in detail earlier. One subject died of a PE 21 days after the 1st dose of Gardasil and was associated with a DVT, but her symptoms preceded the time of vaccination, and she was on OCPs. Another death occurred in a subject with sepsis early in pregnancy that might have been related to an untreated UTI (patient did not take antibiotics), although may have also been related to a post-procedure infection. There was one death associated with a seizure and documented cocaine use. Also, there were 2 MVA associated deaths. There were a similar number of events in the placebo and vaccine groups (4 and 5, respectively).

SAEs: There were 43 reported in the vaccine group and 52 in the placebo group. One SAE of interest was a subject who developed cutaneous vasculitis 10 days after dose 3, whose lab work showed a negative ANA and negative anticardiolipin antibody, and whose symptoms resolved after approximately 1 month.
Most SAEs were related to OB-GYN conditions.

Discontinuations due to AEs: Few subjects in either group discontinued due to an AE (10 in the vaccine group and 8 in the placebo group).

Pregnancy Outcomes

- In all subjects, spontaneous abortions occurred in comparable proportions of vaccinees and placebo recipients in whom the pregnancy outcome was known (26.3% vs. 25.5%, respectively).
- SAEs that occurred in pregnancy were comparable in the two groups (4.2% in the vaccinees and 4.4% in placebo recipients).

Infant SAEs

- Congenital anomalies and timing with relation to vaccination were noted. There were 8 in the vaccine group and 4 in the placebo group (with an additional infant in the placebo group who died in utero). In the vaccine group, 5/8 with congenital anomalies were conceived > 1 month after the time of vaccination in their mothers, while 3/8 in this group were conceived within a month of the time of vaccination in their mothers. No pattern was identified, and the anomalies which occurred in infants when the mothers received Gardasil within 30 days of vaccination included congenital megacolon, talipes equinovarus, and trisomy 21. In the placebo group, all anomalies occurred in infants who were conceived > 1 month after their mothers were vaccinated. See a summary of such events throughout the Phase 3 trials in the safety summary section.
- SAEs in infants during lactation: There were 7 in the vaccine group and 4 in the vaccine group, and most were due to infections (respiratory and GI). See overall safety summary.

8.1.2 Trial #2 (Protocol 013, which includes 2 substudies Protocol 011 and Protocol 012)

Protocol 013: A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particles (VLP) Vaccine in Reducing the Incidence of HPV 6, 11, 16, and 18 Related External Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer in 16-23 Year Old Women (FUTURE I)

Study Period: 12/28/01- 11/4/05
First subject screened 12/29/01.
First subject randomized and vaccinated on 1/30/02 (Protocol 011) and 5/20/02 (Protocol 012). The last visit in the 013 CSR was 7/15/05.
Clean file was achieved 8/11/05, ad the database unblinded 8/12/05.

Protocol 011: Immunogenicity and Safety of Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine in 16-23 year old women when administered alone or concomitantly with Hepatitis B vaccine (Recombinant)
(<u>This is substudy of Protocol 013</u>)

Study Period: 12/28/01 – 6/11/04
Clean file was achieved 9/7/04.
Database unblinded to the unblinded authoring team on 12/7/04.

Protocol 012: Immunogenicity and Safety of Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine in 16-23 Year Old Women with an Immunogenicity Bridge Between the HPV 16 Component of the Quadrivalent Vaccine and the Monovalent HPV 16 Pilot Manufacturing Material
(<u>This is a substudy of Protocol 013</u>)

Study Period: 5/30/02-6/30/04
Clean file (data through Month 7) was achieved 10/13/04
Database was unblinded to the unblinded authoring team on 11/22/04.

(Note: CSR 013v1 was resubmitted in Amendment 0009, 1/13/06, with repagination. The pages referenced in this review are from this version of the clinical study report.)

Protocol 013 Objectives

Protocol 013 Primary Efficacy Objectives

- To demonstrate that a 3 dose regimen of quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18 related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer, and vaginal cancer compared with placebo.
- To demonstrate that a 3 dose regimen of quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 6/11/16/18 related cervical dysplasia (any grade Cervical Intraepithelial Neoplasia [CIN]), Adenocarcinoma in Situ (AIS), or cervical cancer compared with placebo.

Protocol 013 Primary Safety Objective: To demonstrate that a 3 dose regimen of the quadrivalent HPV vaccine is generally well tolerated.

Primary Immunogenicity Endpoints

- **Protocols 011:** To demonstrate that the concomitant administration of quadrivalent HPV vaccine and hepatitis B vaccine does not interfere with the immune response to either vaccine.
- **Protocol 012:** To demonstrate that the Final Manufacturing Process (FMP) material of the quadrivalent HPV vaccine induces a similar anti-HPV 16 response as those induced by administration of the Pilot Manufacturing Material (PMM) HPV 16 vaccine that was used in Protocol 005: Study of PMM lot of HPV 16 VLP Vaccine in Prevention of HPV 16 infection in 16-23 year old women.

Protocol 013 Secondary Efficacy Objectives

- To demonstrate that a 3 dose regimen of the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of HPV 16/18 related cervical dysplasia (any grade CIN), AIS, or cervical cancer compared with placebo.
- To demonstrate that a 3 dose regimen of the quadrivalent HPV vaccine reduces the incidence of the composite endpoint of external genital warts, VIN, VaIN, vulvar cancer or vaginal cancer compared with placebo.

Exploratory Efficacy Objectives (not all listed)

- Impact of the quadrivalent HPV vaccine on the incidence of cervical dysplasia (any grade CIN) compared with placebo.
- Impact of the quadrivalent HPV vaccine on the incidence of definitive therapy (e.g., LEEP and cold knife conization, or definitive wart therapy) compared with placebo.
- To evaluate the relationship between the antibody response to the quadrivalent HPV vaccine and disease endpoints.
- To evaluate persistence of the antibody response to the quadrivalent HPV vaccine (at Month 24).

Design Overview

- This was a randomized, double blind (operating under in-house blinding procedures), placebo controlled, multicenter efficacy study in 5455 subjects. **Each subject was also enrolled in 1 of 2 immunogenicity substudies (Protocol 011, Protocol 012).**
- Papanicolaou (Pap) testing schedule: Day 1, Month 7, Month 12, Month 18, Month 24, Month 30, Month 36 and Month 48, and Pap test abnormalities were followed up according to a pre-defined mandatory triage **algorithm**. (**See Appendix 8.**)
- External genital lesion inspection schedule: Day 1, Month 3, Month 7, Month 12, Month 18, Month 24, Month 30, Month 36 and Month 48, and when a subject presented with symptoms.
- To evaluate immunogenicity, sera were to be obtained at Day 1, Month 7, Month 12, Month 24, and Month 48.
- To evaluate safety, subjects completed a Vaccine Report Card (VRC) for 14 days after each vaccination.

TABLE 78
Protocol 011: Concomitant Hepatitis B Vaccine Administration Substudy

Group	Quadrivalent HPV Vaccine	Hepatitis B Vaccine	Target Enrollment
A	Active	Placebo	450
B	Active	Active	450
C	Placebo	Active	450
D	Placebo	Placebo	450
Total			1800

Source: Table 5-1, CSR 013v1, p. 75

TABLE 79
Protocol 012: Monovalent HPV 16 Bridging Substudy

Group	Vaccination Regimen	Studies in Which the Vaccination group will Participate	Target Enrollment
A	FMP Quadrivalent HPV Vaccine	Monovalent HPV 16 Bridging Substudy, CIN/Warts Efficacy Study	1800
B	PMM Monovalent HPV 16 Vaccine	Monovalent HPV 16 Bridging Substudy	300
C	Placebo	CIN/Warts Efficacy Study	1800
Total			3900

Source: Table 5-2, CSR 013v1, p. 76

Randomization

- Overall, subjects were randomized in a 1:1 ratio to receive either the quadrivalent HPV vaccine or alum placebo.
- At the centers participating in Protocol 011, app. 1800 subjects were randomized in a 1:1:1:1 ratio (Group A, B, C, or D; see above).
- In Protocol 012, 3600 subjects were randomized in a 6:1:6 ratio to Final Manufactured Product (FMP) quadrivalent HPV vaccine, Pilot Manufacturing Material (PMM) monovalent HPV 16 vaccine, or placebo, respectively. Within the FMP quadrivalent vaccine group, subjects were randomized 1:1 to receive one of 2 lots of quadrivalent vaccine.

Vaccine Products Used

TABLE 80
Protocol 011: Vaccine Products Used

Product	Lot Numbers	Contents	Form Supplied
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI0181001	20 mcg HPV 6 L1 VLP/0.5 mL 40 mcg HPV 11 L1 VLP/0.5 mL 40 mcg HPV 16 L1 VLP/0.5 mL 20 mcg HPV 18 L1 VLP/0.5 mL 225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
HPV Placebo	PV501 VAI019A001	225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
Hepatitis B Vaccine (Recombinant)	CV501 VAI002A001	10 mcg HBsAg+500 mcg aluminum adjuvant/1.0 mL	1.2 mL single dose vial
Hepatitis B Placebo	PV501 VAI003P001	420 mcg aluminum adjuvant/1.0 mL	1.2 mL single dose vial

TABLE 81
Protocol 012: Vaccine Products Used

Product	Lot Numbers	Contents	Form Supplied
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI020I001	20 mcg HPV 6 L1 VLP/0.5 mL 40 mcg HPV 11 L1 VLP/0.5 mL 40 mcg HPV 16 L1 VLP/0.5 mL 20 mcg HPV 18 L1 VLP/0.5 mL 225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI020I002	20 mcg HPV 6 L1 VLP/0.5 mL 40 mcg HPV 11 L1 VLP/0.5 mL 40 mcg HPV 16 L1 VLP/0.5 mL 20 mcg HPV 18 L1 VLP/0.5 mL 225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
Monovalent HPV 16 L1 VLP Vaccine	V501 VAI019A001	40 mcg HPV 16 L1 VLP/0.5 mL 225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial
HPV Placebo	PV501 VAI019A001	225 mcg aluminum adjuvant/0.5 mL	0.75 mL single dose vial

Population

- **Protocol 013** was conducted in 62 centers in 16 countries (Austria, Australia, Brazil, Canada, Colombia, Czech Republic, Germany, Hong Kong, Italy, Mexico, New Zealand, Russian Federation, Thailand, United Kingdom, and US and Puerto Rico).
- **Protocol 011** was conducted in 21 study sites in 5 countries in North America (US), Latin America (Brazil, Peru), and Europe (Germany, Czech Republic).
- **Protocol 012** was conducted in 48 study sites in 14 countries in North America (US, Canada, Puerto Rico), Latin America (Colombia, Mexico), Europe (Germany, Austria, Italy, Russian Federation, and the United Kingdom), and Asia-Pacific (Australia, Hong Kong, New Zealand, and Thailaind).

Inclusion Criteria – as noted in Protocol 015 **(Appendix 1),** with additional criterion for Protocol 011 as follows:

- Negative for anti-HBc (qualitative) and anti-HBs (qualitative) within 30 days prior to Dose 1 (Protocol 011 only).

Exclusion Criteria – as noted in Protocol 015 **(Appendix 1)** with additional criteria for Protocol 011 as follows:

- History of previous Hepatitis B infection (Protocol 011 only).
- History of vaccination with any Hepatitis B vaccine (Protocol 011 only).
- Recent administration (within 3 months prior to Day 1) of Hepatitis B immune globulin (Protocol 011 only).
- Any contraindications to hepatitis B vaccine (recombinant) (Protocol 011 only).

Vaccination Schedule

Subjects received vaccine formulation or placebo (0.5 mL) intramuscularly at 0, 2 and 6 months.

Concomitant Vaccines

Hepatitis B (recombinant) Vaccine or placebo was administered with the quadrivalent HPV vaccine in Protocol 011 at Day 0, Month 2 and Month 6.

Endpoints

Protocol 013 Primary Efficacy Endpoints: There are 2 co-primary efficacy endpoints.

- The number of subjects who developed an HPV 6, 11, 16, and/or 18 related external genital lesion. Such an endpoint was met if, on a single biopsy block, HPV 6, 11, 16, or 18 DNA was detected in biopsy thin sections using Merck's PCR assay **AND** the consensus diagnosis of the Pathology Panel was condyloma acuminata, VIN 1, VIN 2/3, VaIN 1, VaIN 2/3, vulvar cancer, or vaginal cancer.
- The number of subjects who developed an HPV 6, 11, 16, and/or 18 related cervical lesion. Such an endpoint was met if, on a single biopsy block, HPV 6, 11, 16, or 18 DNA was detected in biopsy thin sections using Merck's PCR assay **AND** the consensus diagnosis of the Pathology Panel was CIN 1, CIN2, CIN 3, AIS, or cervical cancer.

As in Protocol 015, the primary analysis of vaccine efficacy was conducted in the per-protocol efficacy population, who were naïve to the relevant HPV type. Subjects must have also received all 3 doses of the correct clinical material within 1 year of the Day 1 visit, and must not have violated the protocol that may have interfered with evaluation of the co-primary endpoints.

Secondary Efficacy Endpoints:

- The incidence of the composite endpoint of HPV 16 and 18 related cervical dysplasia (any grade CIN) or HPV 16 and 18 related AIS or cervical cancer.
- The incidence of the composite endpoint of external genital warts, VIN, VaIN, vulvar cancer, or vaginal cancer.

Primary Immunogenicity Endpoints:
Protocols 011:

- GMTs to HPV Types 6, 11, 16, and 18 at Week 4 Postdose 3
- Percentages of subjects who seroconvert (change in serostatus from seronegative to seropositive) for each of 4 HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3. The cut-offs for anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively (as noted in Study 015).
- Percentages of subjects who achieved anti-HBs levels $\geq$ 10 mIU/mL at Week 4 Postdose 3.

Protocol 012:

- Anti-HPV 16 GMTs at Week 4 postdose 3
- Percentage of subjects who seroconverted (change in serostatus from seronegative to seropositive) for HPV 16 by Week 4 postdose 3. The cut-off for anti-HPV 16 seroposivity by cLIA was 20 mMU/L.
- GMTs and seroconversion for HPV 6, 11, and 18 were other parameters of interest.

Exploratory Immunogenicity Endpoints:

- **Protocol 013:** Antibody responses in vaccine recipients who had breakthrough cases of HPV 6, 11, 16, 18 related external genital warts, VIN, or VaIN or HPV 6, 11, 16, 18 related CIN or worse.
- **Protocol 013:** Persistence of antibody over time.
- **Protocol 012:** GMTs and seroconversion for HPV 6, 11, and 18 were other parameters of interest.

Primary Safety Endpoint:
Occurrence of severe injection site adverse events and the incidence of any vaccine related serious adverse experiences.

TABLE 82
Protocol 013: Schedule of Clinical Observations and Laboratory Measurements – (includes Protocols 011 and 012)

Event/Test	Pre-Study	Day 1	Mo 2	Mo 3	Mo 6	Mo 7	Mo 12	Mo 18	**Mo 19** ©	Mo 24	Mo 30	Mo 36	Mo 48
Consent (Protocol 011)	+												
Consent (Protocol 012)		+											
Gyn Hx	+	+				+	+	+	+	+	+	+	+
Gyn PE		+				+	+			+		+	+
Physical Examination		+								+			+
Lab:													
Pregnancy test (a)		+	+		+			+	+	+			
Urine GC (PCR or LCR or SDA)		+					+			+		+	+
Urine chlamydia (PCR or LCR or SDA)		+					+			+		+	+
Serum Ab (b)													
Anti-HPV (6,11,16,18) cLIA*		+				+	+			+			+
Retention serum, stored frozen at study site		+				+	+			+			+
Serum Hep B markers (d)													
Anti-HBs (Quan)		+				+							
Anti-HBs (Qual)	+												
Anti-HBc (Qual)	+												
---------- swabs		+		+		+	(+)	(+)		(+)	(+)	(+)	(+)
Swab for HSV culture (opt)		+				+	+	+		+	+	+	+
Ph Vag fluid (opt)		+				+	+	+		+	+	+	+
Wet mount/trich/BV(opt)		+				+	+	+		+	+	+	+
Whiff test BV (opt)		+				+	+	+		+	+	+	+
KOH for yeast (opt)		+				+	+	+		+	+	+	+
---------- swab		+		+		+	(+)	(+)		(+)	(+)	(+)	(+)
Pap test (Thin Prep) cyto		+				+	+	+		+	+	+	+
Genital Wart Inspection		+		+		+	+	+		+	+	+	+
Vaccination (c)		+	+		+			+	+	+			
Clin f/u for safety (e)		+	+	+	+	+							
Clin f/u safety SAE only								+	+	+			

(+) Specimen must be obtained for optional test by Sponsor

a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)

b. Serum for Ab may be after gyn exam, before vaccination (MRL)
Temp and wt prior to each vaccination

c. Vaccinations for months 18, 19 and 24 are for hepatitis B vaccine placebo recipients to receive Hepatitis B Vaccine (Recombinant) **(Protocol 011-01)**

(d) Applies to Protocol 011

(e). Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. At Months 2, 3, and 7, the study personnel together with the participant will review the VRC. At Months 2, 3, 6, and 7, subjects will be solicited for any gyn health concerns and any SAEs.

*cLIA: Competitive immunoassays developed by MRL using technology from the Luminex Corporation, Austin, TX, USA.

Source: Table 5-2, CSR 011, p. 68-9

Surveillance:
Procedures are noted in the Table above, and similar to those in Protocol 015 (see Surveillance in Protocol 015). Differences are noted below.

- For **Protocol 011 only**, a preliminary screening visit was performed prior to the first vaccination to assess anti-hepatitis B core antigen (qualitative) and anti-hepatitis B surface antigen (qualitative) to determine eligibility for inclusion in the study. Only subjects negative for both were enrolled in the study.
- Vaccine or placebo was administered IM at Day 0, Month 2 and Month 6.
- In **Protocol 011,** Hepatitis B vaccine or placebo were administered at the same times. If the subject received Hepatitis B placebo in the primary series, they would be offered Hepatitis B vaccine at Months 18, 19, and 24.
- **HPV DNA by PCR:** Testing of additional genital swabs for HPV types obtained at Months 12, 18, 24, 30, 36, and 48 was optional.
- **For Protocol 011**, hepatitis B serology testing outside the study prescribed time period was to have been avoided due to unblinding concerns unless there was a strong clinical indication.
- **Ascertainment of HPV Related External Genital Lesions:** A genital wart examination, including an exam of the vaginal walls, at baseline (Day 1), Months 3, 7, 12, 18, 24, 30, 36, and 48 at the completion of the pelvic examination, following collection of all specimens. Symptomatic subjects may be seen at unscheduled visit for evaluation. All new lesions that were possibly, probably or definitely HPV related were to be biopsied. If the lesion was definitely not HPV related, the lesion was not biopsied. If a suspect lesion was identified, a biopsy specimen was to be obtained and submitted to the central lab for analysis. Photographs of any new external genital lesions were to be obtained irrespective of whether the lesion was biopsied.
- **Ascertainment of HPV Related Cervical Lesions:** A ThinPrep Pap test specimen for cytology was collected at Day 1, and Months 7, 12, 18, 24, 30, 36 and 48 and at any unscheduled visit that the investigator deemed necessary to obtain a sample. All ThinPrep Pap tests were analyzed at a central cytology lab chosen by the sponsor. Cytology specimens were evaluated using The Bethesda System-2001. For all cytology diagnoses of ASC-US, the lab automatically performed reflex HPV testing on residual ThinPrep material, using the Digene Hybrid Capture II, High Risk/Low Risk Probes (Digene).

Colposcopy Algorithm (based on Pap test results):

- The study had mandatory guidelines for referral to colposcopy and biopsy which was slightly different than the one used in Protocol 015. Any deviation required approval by the Medical Monitor. Protocol 013 contained the same requirements for colposcopists as noted in Protocol 015. **(See Appendix 8)**

Reviewer's Comment: The colposcopy algorithm was slightly different from that in Protocol 015 regarding the management of ASC-US. In **Protocol 013**, for ASC-US, the central lab performed reflex HPV testing for High Risk and Low Risk HPV types. If at least 1 probe was positive, the subject was to be referred to colposcopy. If both probes were negative, the subject was returned for Pap at the routine screening visit. In **Protocol 015**, if there was ASC-US or LSIL, the subject would return for a Pap in 6 months,

except if LSIL was noted at Day 1 or Month 48, which would trigger an immediate colposcopy. If the repeat Pap showed LSIL, ASC-H, AGC, or HSIL, the subject would have a colposcopy. If the repeat Pap showed ASC-US, reflex HPV testing would be performed as above, and colposcopy performed if one probe was positive for HR HPV.

The Sponsor notes that ascertainment in Protocol 013 was aggressive to provide maximum sensitivity for detection of HPV related cervical lesions. The colposcopy referral was set low (ASC-US with positive low-risk HPV HC II probe) maximizing the likelihood for detection of HPV related cervical lesions.

Safety Follow-up was similar to that noted in Protocol 015 for the Detailed Safety Cohort.

Statistical Considerations for Efficacy:
Primary Efficacy Objectives:

- The number of cases of **external genital lesions** related to HPV 6, 11, 16, and 18 were defined as the number of cases of subjects with $\geq$ 1 of the following: Pathology panel consensus diagnosis of genital warts, VIN 1, VIN 2, VIN 3, VaIN 1, VaIN 2, VaIN 3, vulvar cancer and vaginal cancer **AND** HPV 6, 11, 16, or 18 detected by thin-section PCR in an adjacent section from the same tissue block.
- The **number of cervical lesions** related to HPV 6, 11, 16, and 18 were defined as the number of cases of subjects with $\geq$ 1 of the following: Pathology panel consensus diagnosis of CIN 1, CIN 2, CIN 3, AIS, or cervical cancer **AND** HPV 6, 11, 16, or 18 detected by Thinsection PCR in an adjacent section from the same tissue block.
- Tests of the co-primary efficacy hypotheses were predicated on at least 38 cases of HPV 6, 11, 16, or 18 related external genital warts and at least 38 cases of HPV 6, 11, 16, or 18 related CIN being observed in this study. The sample size provided the study 91% power to declare the vaccine efficacious against each endpoint with a 2-sided alpha = 0.025.
- Follow-up of the primary efficacy endpoints began following the Month 7 visit.
- The co-primary efficacy hypotheses for the individual trial were tested using a one-sided test of the null hypothesis that vaccine efficacy was 20% or less. The alternative hypothesis was that the vaccine was efficacious relative to placebo (i.e., VE >20%).
- For subjects who became cases, the final visit date was the visit date at which external genital warts, VIN, VaIN, CIN or cancer was detected. If a subject developed more than one case of a given endpoint, the final visit date was the date at which the first case of the endpoint was detected. For subjects who were non-cases, the final visit date for the external genital lesion endpoint was the date representing the last opportunity to observe an external genital endpoint, defined as the later of the last scheduled visit and the last unscheduled visit at which an external genital exam or biopsy was performed. The final visit date for subjects who were non-cases for the CIN endpoint was the date representing the last opportunity to observe a cervical endpoint, defined as the latest of the subject's cervical specimens (biopsies, ECCs, definitive therapies and Pap tests).
- For the purposes of subject accounting for the primary analyses, subjects were regarded as having completed the immunogenicity study if they had completed the

full vaccination regimen (3 doses) and they had completed the follow-up visit at Month 7 (including serum and PCR specimen collection). Subjects were regarded as having completed the efficacy study if they had completed the full vaccination regimen (3 doses) and they had completed follow-up visits through the time at which the required numbers of cases of the primary efficacy endpoints are observed, or when the 48 month visit was completed, which ever comes first (unless an abnormal ThinPrep Pap test at 48 months requires additional visits).

Efficacy Analysis Populations:
The primary approach to the analysis of efficacy was per protocol. Several modified intent to treat (MITT) populations were also considered as in Study 015. (Please see **Appendix 4.)** The only additional population in Study 013 was the MITT-4 population, with the definition below.

TABLE 83
Definition of MITT-4 Population

Efficacy Population	Definition
MITT-4	*Received at least 2 vaccinations *Were seronegative at Day 1 to the relevant HPV types and PCR negative Day 1 through Month 3 for the relevant HPV types *Cases were counted starting 30 days after 2nd vaccination.

Secondary Efficacy Objectives:

- At the time of the primary analysis, 18 cases of the secondary endpoint of HPV 16/18 related CIN were expected. Assuming the true VE of at least 80%, conducting the test of the secondary efficacy hypothesis regarding HPV 16/18 related CIN at the time of the primary analysis would provide the study 83.2% power to declare the vaccine efficacious against HPV 16/18 related CIN with a 2 sided alpha of 0.05.
- At the time of the primary analysis, 67 cases of the secondary endpoint of external genital warts/VIN/VaIN due to any HPV type were expected. Assuming true VE of 70%, conducting the test of the secondary analysis hypothesis regarding this endpoint would provide the study 99.7% power to declare the vaccine efficacious against external genital warts/VIN/VaIN with a 2-sided alpha = 0.05.

Handling of Dropouts or Missing Data: The same 2 methods were used as in Protocol 015.

Eligibility for Analysis Populations
If, for a given HPV type, the PCR result from a biopsy sample taken between enrollment and Month 7 (inclusive) was missing for a given vaccine HPV type, and the biopsy was diagnosed as normal, the subject *was* eligible. (This rule was established because abnormal tissue is likely to be HPV PCR positive and is as noted in Protocol 015.)

Missing Data During Efficacy Follow-up
Biopsy, ECC, or LEEP/conization specimens missing PCR result or Pathology Panel diagnosis were not used to classify a subject as a case. Subjects who had a definitive

therapy procedure without becoming a case of CIN were censored for the analyses of the cervical endpoints at the time of the definitive therapy procedure.

Statistical Considerations for Immunogenicity Analyses:
Protocol 011: Success was required for all three co-primary immunogenicity hypotheses.
Similar anti-HPV 6, 11, 16, 18 antibody responses to quadrivalent HPV vaccine given with or without Hepatitis B vaccine.

- **GMTs** to HPV 6, 11, 16, or 18 at Week 4 Postdose 3 of HPV vaccine, given with or without Hepatitis B vaccine. The sponsor's statistical criterion for similarity required that the lower bound of the confidence interval for the fold-difference in GMTs between the 2 groups [(HPV + hepatitis B vaccine]/ [HPV + placebo)] exclude a decrease of 2-fold or more for each HPV type.
- **Percentage of subjects who seroconvert** for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3 of HPV vaccine, given with or without Hepatitis B vaccine. The sponsor's statistical criterion for similarity required that the lower bound of the confidence interval for the difference in proportions between the 2 groups [(HPV vaccine + hepatitis B vaccine) - (HPV vaccine + placebo)] exclude a decrease of 5 percentage points or more for each HPV type.

NI anti-HBs antibody responses to Hepatitis B vaccine given with or without HPV vaccine.

- **Percentage of subjects who achieve anti-HBs levels $\geq$ 10 mIU/mL** at Week 4 Postdose 3 of Hepatitis B vaccine, given with or without HPV vaccine. The sponsor's statistical criterion for NI requires that the lower bound of the confidence interval for the difference in proportions between the 2 groups [(hepatitis B vaccine [recombinant] + HPV) - (hepatitis B vaccine [recombinant]+ placebo)] exclude a decrease of 10 percentage points or more).

Protocol 012: Success was required for co-primary immunogenicity hypotheses.
FMP Quadrivalent HPV vaccine induces NI anti-HPV 16 immune responses as with PMM Monovalent HPV 16 vaccine

- **GMTs** to HPV 16 at week 4 postdose 3 of FMP quadrivalent HPV vaccine and PMM monovalent HPV 16 vaccine were compared. The sponsor's statistical criterion for NI requires that the LB of the CI for the fold-difference in proportions between the 2 groups (FMP quadrivalent/PMM HPV 16) exclude a decrease of 2-fold or more.
- FMP quadrivalent HPV vaccine induces NI immune response, as measured by the percentage of subjects who seroconvert for HPV 16 by Week 4 postdose 3, to that induced by PMM HPV 16 vaccine. Seroconversion was a change in serostatus from seronegative to seropositive, and a subject was considered seropositive with an anti-HPV 16 GMT of $\geq$ 20 mMU/L. The statistical criterion for NI requires that the LB of the CI for the difference in proportions between the 2 groups (FMP quadrivalent – PMM HPV 16) exclude a decrease of 5% points or more.

Protocol 013: Anti-HPV 6, 11, 16, and 18 GMTs and the corresponding 95% CIs were calculated at Day 1 and Months 7 and 24. Seropositivity rates and the corresponding 95% CIs for HPV 6, 11, 16, and 18 were also computed.

Immunogenicity Populations:

TABLE 84
Definitions of Immunogenicity Populations for Protocols 011 and 012

Efficacy Population	Definition
Per Protocol Imunogenicity Population Protocol 011	*Received all 3 vaccinations *Sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Did not deviate from protocol
Per Protocol Imunogenicity Population Protocol 012	*Received all 3 vaccinations *Sero- and PCR negative at Day 1 and PCR negative through Month 7 for HPV 16 *Did not deviate from protocol
All Type Specific HPV Naïve Subjects with Serology Data Population Protocol 011	*Sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Had a valid serology result after the 3rd vaccination *Included protocol violators
All Type Specific HPV 16 Naïve Subjects with Serology Data Population Protocol 012	*Sero- and PCR negative at Day 1 and PCR negative through Month 7 for HPV 16 *Had a valid serology result after the 3rd vaccination *Included protocol violators
All Subjects with Serology Data Population	*Included all subjects who had valid anti-HBs (quantitative) serology results after the 3rd vaccination *Included protocol violators

Statistical Considerations for Safety Analyses:

- All subjects who received at least one injection and had follow-up data were included in the safety summary.
- Subjects who received mixed regimens were excluded from statistical analyses and presented separately by the sponsor.
- Risk differences and associated exact 95% confidence intervals were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with $\geq$ 1% incidence in either vaccination group.
- Elevated temperatures ($\geq$100°F [$\geq$ 37.8°C], oral equivalent) within 5 days following each vaccination were summarized in a similar manner.

Changes in Protocol 013 and Changes in Statistical Analysis: Three amendments to the protocol were submitted to the IND and reviewed prior to unblinding. Several changes were made to the planned statistical analysis prior to unblinding and did not result in major changes to protocol conduct. See **Appendix 9** for details**.**

Protocol 013 Results
Protocol 013: Populations Enrolled/Analyzed

TABLE 85
Protocol 013: Subject Disposition

	Vaccine	Placebo	Total
Subjects screened but not enrolled (failure to meet I/E criteria)			1008
Randomized	2723	2732	5455
Randomized Subjects who did not receive vaccination			13
Reasons for non-vaccination:			
Pt. discontinued for other			1
Pt. withdrew consent			4
Protocol deviation			8
	n/%	n/%	n/%
Vaccinated at:			
Dose 1	2717 (99.8%)	2725 (99.7%)	5442 (99.8%)
Dose 2	2654 (97.5%)	2656 (97.2%)	5310 (97.3%)
Dose 3	2600 (95.5%)	2599 (95.1%)	5199 (95.3%)
Vaccination Period (Day 1 through Month 7)			
Entered	2717	2725	5442
Completed	2582 (95.0%)	2586 (94.9%)	5168 (95.0%)
Discontinued	135 (5.0%)	139 (5.1%)	274 (5.0%)
With Long Term Follow-up	15 (0.6%)	13 (0.5%)	28 (0.5%)
Clinical AE	0 (0.0%)	4 (0.1%)	4 (0.1%)
Other Reasons	10 (0.4%)	1 (0.0%)	11 (0.2%)
Pregnancy	5 (0.2%)	8 (0.3%)	13 (0.2%)
Without Long Term Follow-up	120 (4.4%)	126 (4.6%)	246 (4.5%)
Clinical AE	2 (0.1%)	3 (0.1%)	5 (0.1%)
Lost to follow-up	48 (1.8%)	44 (1.6%)	92 (1.7%)
Moved	14 (0.5%)	18 (0.7%)	32 (0.6%)
Other reasons	2 (0.1%)	1 (0.0%)	3 (0.1%)
Withdrew Consent	54 (2.0%)	60 (2.2%)	114 (2.1%)
Follow-Up Period (After Month 7)			
Entered	2592	2595	5187
Continuing	2536 (97.8%)	2537 (97.8%)	5073 (97.8%)
Discontinued	56 (2.2%)	58 (2.2%)	114 (2.2%)
Clinical AE	1 (0.0%)	1 (0.0%)	2 (0.0%)
Lost to follow-up	30 (1.2%)	30 (1.2%)	60 (1.2%)
Moved	9 (0.3%)	6 (0.2%)	15 (0.3%)
Withdrew Consent	16 (0.6%)	21 (0.8%)	37 (0.7%)

Source: Table 6-1, CSR 013v1, p. 169-70

Protocol 011: Populations Enrolled/Analyzed

TABLE 86
Protocol 011: Subject Disposition

	HPV Vaccine + Hep B Vaccine	HPV Vaccine + Hep B Placebo	HPV Placebo + Hep B Vaccine	HPV Placebo + Hep B Placebo	Total
Screened but not randomized (failure to meet I/E criteria)					649
Randomized	468	471	467	471	1877
Randomized but not vaccinated	2	3		1	6
Pt. withdrew consent	1	1		0	
Protocol Deviation	1	2		1	
	n/%	n/%	n/%		
Vaccinated at:					
Dose 1	466 (99.6%)	468 (99.4%)	467 (100.0%)	470 (99.8%)	1871 (99.7%)
Dose 2	454 (97.0%)	459 (97.5%)	456 (97.6%)	465 (98.7%)	1834 (97.7%)
Dose 3	445 (95.1%)	456 (96.8%)	449 (96.1%)	459 (97.5%)	1809 (96.4%)
Vaccination Period (Day 1 through Month 7)					
Entered	446	468	467	470	1871
Completed	443 (95.1%)	454 (97.0%)	446 (95.5%)	459 (97.7%)	1802 (96.3%)
Discontinued	19 (4.1%)	12 (2.6%)	20 (4.3%)	9 (1.9%)	60 (3.2%)
With Long Term Follow-up	1 (0.2%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	3 (0.2%)
Clinical AE	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Pregnancy	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.1%)
Without Long Term Follow-up	18 (3.9%)	12 (2.6%)	18 (3.9%)	9 (1.9%)	57 (3.0%)
Clinical AE	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Lost to follow-up	6 (1.3%)	6 (1.3%)	6 (1.3%)	2 (0.4%)	20 (1.1%)
Moved	4 (0.9%)	1 (0.2%)	4 (0.9%)	2 (0.4%)	11 (0.6%)
Withdrew Consent	8 (1.7%)	5 (1.1%)	7 (1.5%)	5 (1.1%)	25 (1.3%)

From Table 6-1, CSR 011, p. 119

Protocol 012: Populations Enrolled/Analyzed

TABLE 87
Protocol 012: Subject Disposition

	FMP Quadrivalent HPV Vaccine	PMM HPV 16 Vaccine	Placebo	Total
Screened but not enrolled (failure to meet I/E criteria)				359
Randomized	1784	304	1794	3882
Randomized but not vaccinated	1		6	7
Pt. discontinued for other	0		1	1
Pt. withdrew consent	0		2	2
Protocol deviation	1		3	4
	n/%	n/%	n/%	n/%
Vaccinated at:				
Dose 1	1783 (99.9%)	304 (100.0%)	1788 (99.7%)	3875 (99.8%)
Dose 2	1741 (97.6%)	298 (98.0%)	1735 (96.7%)	3774 (97.2%)
Dose 3	1699 (95.2%)	293 (96.4%)	1691 (94.3%)	3683 (94.9%)
Vaccination Period (Day 1 through Month 7)				
Entered	1783	304	1788	3875
Completed	1683 (94.4%)	290 (95.4%)	1680 (94.0%)	3653 (94.3%)
Discontinued	97 (5.4%)	13 (4.3%)	101 (5.6%)	211 (5.4%)
With Long Term Follow-up	13 (0.7%)	0 (0.0%)	10 (0.6%)	23 (0.6%)
Clinical AE	0 (0.0%)	0 (0.0%)	3 (0.2%)	3 (0.1%)
Other Reasons	9 (0.5%)	0 (0.0%)	1 (0.1%)	10 (0.3%)
Pregnancy	4 (0.2%)	0 (0.0%)	6 (0.3%)	10 (0.3%)
Without Long Term Follow-up	84 (4.7%)	13 (4.3%)	91 (5.1%)	188 (4.9%)
Clinical AE	2 (0.1%)	0 (0.0%)	2 (0.1%)	4 (0.1%)
Lost to follow-up	31 (1.7%)	5 (1.6%)	29 (1.6%)	65 (1.7%)
Moved	8 (0.4%)	1 (0.3%)	11 (0.6%)	20 (0.5%)
Other reasons	2 (0.1%)	0 (0.0%)	1 (0.1%)	3 (0.1%)
Withdrew Consent	41 (2.3%)	7 (2.3%)	48 (2.7%)	96 (2.5%)

From Table 6-1, CSR 012, p. 103

TABLE 88
Protocol 013: Subjects Enrolled by Region

Region	Screening Failures	Number Randomized	Quadrivalent HPV Vaccine	Placebo
Asia-Pacific	12	521	257	264
Europe	60	1122	563	559
Latin America	713	2215	1107	1108
North America	223	1597	796	801
Total	1008	5455	2723	2732

Source: From Tables 11-1, 11-2, 11-3, 11-4, CSR 013v1, p. 433-440

Efficacy and Immunogenicity Populations Analyzed- Protocol 013

- A total of 3,996 [73%] HPV 6/11, 3,771 [69%] HPV 16, and 4,286 [78%] HPV 18 subjects were eligible to be included in the per protocol analysis. The proportions of the overall study population included in the PPE populations for each HPV type were comparable between the 2 groups.

- The most common reason for exclusion from each of the HPV 6/11, HPV 16, and HPV 18 PPE populations was positivity to the relevant HPV type between Day 1 through Month 7, and the numbers were generally comparable between the vaccine and placebo groups for each PPE population. There were 724/2717 Gardasil recipients and 722/2725 placebo recipients excluded from the HPV 6/11 PPE population; 813/2717 Gardasil receipients and 858/2725 placebo recipients excluded from the HPV 16 PPE population; and 581/2717 Gardasil recipients and 575/2725 placebo recipients excluded from the HPV 18 PPE population. (Source: Table 6-3, CSR 9013v1, p. 174-7, not shown here)

TABLE 89
Protocol 013: Number of Subjects with Efficacy Phase Follow-up in the Per Protocol Efficacy Population by Vaccination Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=2,723)	Placebo (N=2,732)	Total (N=5,455)
HPV 6/11 PPE Population	1,993	2,003	3,996
HPV 6/11-Related CIN Endpoint			
Subjects With Post Month 7 Follow-Up	1,960	1,975	3,935
Subjects Without Post Month 7 Follow-Up	33	28	61
HPV 6/11-Related EGL Endpoint			
Subjects With Post Month 7 Follow-Up	1,978	1,991	3,969
Subjects Without Post Month 7 Follow-Up	15	12	27
HPV 16 PPE Population	1,904	1,867	3,771
HPV 16-Related CIN Endpoint			
Subjects With Post Month 7 Follow-Up	1,887	1,847	3,734
Subjects Without Post Month 7 Follow-Up	17	20	37
HPV 16-Related EGL Endpoint			
Subjects With Post Month 7 Follow-Up	1,890	1,855	3,745
Subjects Without Post Month 7 Follow-Up	14	12	26
HPV 18 PPE Population	2,136	2,150	4,286
HPV 18-Related CIN Endpoint			
Subjects With Post Month 7 Follow-Up	2,101	2,120	4,221
Subjects Without Post Month 7 Follow-Up	35	30	65
HPV 18-Related EGL Endpoint			
Subjects With Post Month 7 Follow-Up	2,120	2,136	4,256
Subjects Without Post Month 7 Follow-Up	16	14	30

Source: Table 6-4, CSR 013v1, p. 178

Immunogenicity Population Analyzed: Protocol 011

- 76 (4.1%) of subjects were excluded from the PPI analysis because of HepBsAb positivity at Day 1. The assay used at Day 1 was a quantitative assay that identified more seropositive subjects than the qualitative assay used at screening.

- The most common reason for exclusion from the PPI analyses was positivity to HPV 16, 6/11, or 18. The most common reasons for exclusion for exclusion from the Hepatitis B PPI analyses were: vaccination 2 or 3 out of day ranges, and Month 7 serology sample out of day range. The number of subjects excluded from each group was generally comparable. (Source: Tables 6-2, 6-3, CSR 011, p. 121-5, not shown here)

Immunogenicity Populations Analyzed-Protocol 012

- The proportions of subjects in all exclusion categories appear to be balanced among the 3 vaccination group.
- Reasons for exclusion were similar to Protocol 013.

Demographic and Baseline Characteristics-Protocol 013

- The 62 sites were located in 16 countries in North America, Latin America, Europe, and Asia-Pacific.
- In **Protocol 011**, there were 21 sites in 5 countries. There were 144 subjects in the US; 364 subjects in Europe (Germany and Czech Republic); 1369 in Latin America (Brazil and Peru). (Source: Table 6-4, CSR 011, p. 127).
- In **Protocol 012**, there were 48 sites in 14 countries. There were 1572 subjects in North America (US, Puerto Rico, Canada); there were 856 subjects in Europe (Germany, Austria, Italy, Russian Federation, UK); there were 567 subjects in Asia Pacific (Australia, Hong Kong, New Zealand, Thailand); and there were 917 subjects in Latin America (Colombia and Mexico). (Source: Table 6-4, CSR 012, p. 109-110)

Basic Subject Characteristics-Protocol 013

- The vaccine and placebo groups were well balanced with regard to age, ethnicity, and smoking status.
- Mean age: 20.3 years (median 20 years).
- Of 5455 subjects in total, the majority of subjects were white (3158 [57.9%]); 1133 (20.8%) were Hispanic American; 525 (9.6%) were other; 316 (5.8%) were Asian; 303 (5.6%) were black; and 20 (0.4%) were Native American. (Source: Table 6-6, CSR 013v1, p. 185, not shown here)
- 6 subjects received protocol non-compliant treatments

Sexual Demographics-Protocol 013

- Overall, 95.6% of subjects had experienced sexual debut prior to study onset.
- The median age of first intercourse among non-virgins was 17 years and the median number of sexual partners was 2. (Source: Table 6-7, CSR 013v1, p. 188)
- Comparison of the 4 geographic regions:
  - Subjects from Asia had a slightly higher mean age of sexual debut compared to the other regions (17.7 years).
  - Within the regions, the sexual demographics were comparable between the 2 groups. (Source: Tables 11-12, 11-13, 11-14, 11-15, CSSR 013v1, p. 462-69, not shown here)

Gynecologic History-Protocol 013

- Overall, the most frequent gynecologic procedure at enrollment was vaginal or vulvar surgery (8.6%).
- The most frequent genital tract infection was vaginal candidiasis (9.8%), followed by bacterial vaginosis (6.8%) and Chlamydia trachomatis (5.4%). These were generally comparable between the groups. (Source: Table 6-8, CSR 013v1, p. 191, not shown here)
- More subjects in Latin America (28.2%) and Asia (14.4%) reported having had a procedure than in Europe (2.9%) or North America (6.2%). The most common procedure in Latin America was vaginal or vulvar surgery (19.0%), and those in Asia had a higher percentage with dilatation and extraction (13.2%). (Source: Tables 11-17, 11-18, 11-19, 11-20, CSR 013v1, p. 472- 476, not shown here)

Non-HPV cervicovaginal infections at Day 1-Protocol 013

- App. 5.3% had such an infection, and the most common one was Chlamydia (4.7%).
- The vaccination groups were fairly comparable (although there was a slightly higher percentage [5.6%] in the placebo group with a non-HPV cervicovaginal infection compared to the Gardasil group [5.0%]. (Source: Table 6-9, CSR 013v1, p. 194, not shown here)

Pregnancy history – Protocol 013

- Overall, 72% of subjects reported no prior pregnancy. (Source: Table 6-10, CSR 013v1, p. 196, not shown here)

Contraceptive use prior to Day 1 – Protocol 013

- The percentages were comparable in the vaccine and placebo group. (Source: Table 6-11, p. 199-201 and Table 11-31, p. 492-3, CSR 013v1, not shown here)
- Subjects in Latin America were more likely to use abstinence and less likely to use hormonal contraception. Subjects in Europe were more likely to use hormonal contraceptives (app. 74-78%), and subjects in Asia were more likely to use barrier contraceptives (app. 37%-41%). Within each region, the proportions of subjects in each treatment group were comparable. (Source: Tables 11-32, 11-33, 11-34, 11-35, CSR 013v1, p. 494-51, not shown here)

HPV Related Pathology at Day 1 – Protocol 013

- In the PPE population, among subjects with a satisfactory Pap test result, app. 89% were negative for SIL at baseline.
- Among subjects with SIL at baseline, the most common diagnosis was LSIL (11.4%), with the second most common diagnosis ASC-US (4.4%). There were slightly more subjects with ASC-US (4.9%) and LSIL (6.3%) in the placebo group compared to the vaccine group (3.9% and 5.9%, respectively). (Source: Table 6-12, CSR 013v1, p. 203, not shown here)
- In Asia, SIL was present in a lower percentage of subjects (8.0%) compared to the other regions. In Latin America, the percentage of subjects with SIL was slightly higher than that seen overall (12.6%). Within each region, the proportions of subjects with an SIL diagnosis were generally comparable. (Source: Tables 11-37, 11-38, 11-39, 11-40, CSR 013v1, p. 503-6, not shown here)

HPV 6, 11, 16, 18 Serostatus and DNA Detection at Day 1 – Protocol 013

- In the vaccination groups, app. 20% were positive to a vaccine HPV type by serology, and approximately 14% were positive by PCR.
- App. 27% were positive by either serology or PCR. (Source: Table 6-13, CSR 013v1, p. 205, not shown here) This information is also presented for the 4 geographic regions.
- Overall, positivity to HPV 6, 11, 16, or 18 by either serology or PCR was highest in Latin America (app. 32%) and lowest in Asia-Pacific (app. 17%). In North America and Europe, the overall positivity was app. 24-25%. Within a region, the proportions of subjects who were positive by serology and/or PCR were comparable between the 2 vaccination groups. (Source: Tables 11-41, 1-42, 11-43, 11-44, CSR 013v1, p. 507-10, not shown here)
- The proportion of subjects found to be HPV 6, HPV 11, HPV 16, or HPV 18 seropositive were comparable between the 2 vaccination groups. Of the immune responses to the 4 vaccine HPV types, anti-HPV 16 baseline seropositivity was the most common (11.6%) and anti-HPV 11 baseline seropositivity was the least common (2.2%). HPV 6 seropositivity was 7.4% and HPV 18 seroposivity was 3.4% overall. (Source: Table 6-14, CSR 013v1, p. 207-8, not shown here) Generally, seropositivity was more prevalent than PCR positivity.

HPV 6, 11, 16, 18 DNA Detection at Day 1 – Protocol 013

- The vaccination groups were generally comparable with regard to the overall proportion of subjects in whom vaccine type HPV DNA was detected, as well as the proportion of subjects in whom specific vaccine HPV types were detected.
- The prevalence of HPV 16 DNA (8.6%) positivity was highest, and lowest for HPV 11 DNA (0.6%). HPV 6 DNA was seen in 3.6%, and HPV 18 DNA in 3.1%, overall. (Source: Table 6-15, CSR 013v1, p. 210, not shown here)
- PCR positivity was generally similar in Europe, Latin America, and North America, but somewhat lower in Asia. Within a region, the proportions of subjects with vaccine HPV DNA were comparable between the 2 vaccine groups. (Source: Tables 11-49, 11-50, 11-51, 11-52, CSR 013v1, p. 519-22, not shown here)
- **Detection of Multiple Vaccine HPV Types at Day 1**: The 2 vaccination groups were generally balanced with regard to the proportions of subjects in whom DNA for more than one vaccine HPV type was detected. Of the 4 vaccine types, the most common co-infections were with HPV 6 and HPV 16 (0.9% of subjects), followed by infection with HPV 16 and HPV 18 (0.7% of subjects), and followed by infection with HPV 6 and 18 (0.2%). Very few subjects (0.1%) overall had 3 or more HPV types identified. (Source: Table 6-16, CSR 013v1, p. 212, not shown here)

Prior Medication and Prior Vaccines: These were provided in CSR 011 and 012.

- Similar medication use was noted in the time prior to vaccination in both protocols.
- Hormonal contraceptives were the most often reported medication in the 3 days prior to vaccination in both protocols (46-62%) (Source: Table 6-16, p. 155-6 and Appendix 4.5, 2730-41, CSR 011; and Table 6-16, p. 129-30 and Appendix 4.5, p. 2630-51, CSR 012, not shown here)

Concomitant Medications and Vaccines: These were also provided in CSR 011 and 012. Similar medication use was noted in both studies.

- Approximately 90-92% of subjects overall received concomitant therapy.
- Hormonal contraceptives were the most often used medications (68-83%). (Source: Table 6-17, CSR 011, p. 158 – 161 and Table 6-18, CSR 012, p. 133-136, not shown here)

Prior Medical History – Protocol 013

- The most commonly reported medical problems included dysmenorrhea and headache.
- The proportions of subjects with specific medical conditions prior to visit 1 were generally comparable between the 2 treatment groups. (Source: Table 6-17, p. 215-21 and Table 11-57, p. 531-593, CSR 013v1, not shown here)

Treatment Compliance – Protocol 013

- The majority of subjects in both groups received the second and third doses of study material within 3 weeks from the scheduled time. (Source: Figures 6-2 and 6-3, CSR 013v1, p. 223-4, not shown here)
- **Completion of Scheduled Visits During Efficacy Follow-up Period:** App. 96% of subjects completed the Month 7 visit; 94-95% completed the Month 12 visit; 93% completed the Month 18 visit; 90% completed the Month 24 visit; and 55% completed the Month 30 visit. Very few subjects in the study report had a Month 36 visit (app. 3%) because the primary analysis occurred before this visit. (Source: Table 6-18, CSR 013v1, p. 225 not shown here)

Protocol 013 Efficacy Results

- The **primary efficacy analysis** was to occur when at least **38 subjects had developed HPV 6, 11, 16, or 18 related external genital disease and** at least **38 cases of HPV 6, 11, 16, or 18 related CIN, AIS, or cervical cancer** were detected.
- Separately, efficacy data from Protocol 013 were to be combined with efficacy data from Protocols 005, 007, and 015 in a prespecified analysis to evaluate vaccine efficacy with respect to the combined incidence of **HPV 16 or 18 related CIN 2/3. AIS, or cervical cancer**. The combined analysis was to be performed when there were **at least 33 women with these conditions across the 4 studies.** There were **19 cases of HPV 16 or 18 related CIN 2/3, AIS or cervical cancer** in Protocol 013, which brought the total number to **53 cases** across the 4 studies. There were **40 cases of HPV 6, 11, 16, 18 related EGL** and **37 cases of HPV 6, 11, 16, 18 related CIN, AIS or cervical cancer** (through 7/15/05) in Protocol 013.

The sponsor notes that the remainder of the trial will be an extension study, with those responsible for ascertainment of cases, such as study staff and lab personnel, will remain blinded as to treatment allocation.

Subjects Contributing to the Analyses of Cervical Endpoints vs. External Genital Endpoints: This is as noted in Protocol 015.

Counting Individual Endpoints within Composite Endpoints – see Appendix 6

Prophylactic Efficacy

Tests of Co-Primary Hypotheses

- The observed VE against both co-primary endpoints (6, 11, 16, or 18 related CIN and 6, 11, 16, or 18 related EGLS) was 100%, with a LB of the 95% CI substantially > 20%.
- With regard to the CIN endpoint, there were no cases of cervical cancer.
- Subjects contributing to the primary analyses had an average of 1.7 person-years of follow-up through the Month 7 visit for each of the co-primary endpoints.

TABLE 90
Protocol 013: Primary Efficacy Analysis Against HPV 6/11/16/18 related CIN and External Genital Lesions (Per-Protocol Efficacy Analysis)

	Gardasil N=2717				Placebo N=2725						p-value
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI	
HPV 6/11/16/18 Related CIN	2240	0	3779.8	0	2258	37	3787.4	1.0	**100%**	87.4, 100.0%	< 0.001
HPV 6/11/16/18 Related EGL	2261	0	3865.2	0	2279	40	3787.4	1.0	**100%**	88.4, 100.0%	< 0.001

Source: Table 7-3, CSR 013v1, p. 240

Analyses of Vaccine Efficacy Against HPV 6/11/16/18 related CIN

Efficacy Against HPV 6, 11, 16, 18 related CIN in the PPE Population

- In the PPE population, there was evidence of efficacy of Gardasil againt CIN related to each of the vaccine HPV types, and against the different grades of CIN. It is noted that the point estimates of efficacy against HPV 11 related CIN and vaccine HPV related AIS were each 100%, although these did not reach statistical significance because of small numbers. (See Table 91 below).

TABLE 91
Protocol 013: Efficacy Analysis Against HPV 6/11/16/18 Related CIN by HPV Type amd Severity (PPE Population)

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related CIN	2240	0	3779.8	0.0	2258	37	3787.4	1.0	**100.0%**	87.4, 100.0%
By HPV Type										
HPV 6 Related CIN	1960	0	3316.0	0.0	1975	7	3332.6	0.2	**100.0%**	30.3, 100.0%
HPV 11 Related CIN	1960	0	3316.0	0.0	1975	3	3334.9	0.1	**100.0%**	<0.0, 100.0%
HPV 16 Related CIN	1887	0	3201.0	0.0	1847	22	3130.6	0.7	**100.0%**	82.1, 100.0%
CIN 18 Related CIN	2101	0	3557.9	0.0	2120	8	3569.1	0.2	**100.0%**	41.2, 100.0%
By Lesion Type										
CIN 1	2240	0	3779.8	0.0	2258	25	3789.7	0.7	**100.0%**	84.1, 100.0%
CIN 2 or worse	2240	0	3779.8	0.0	2258	20	3794.4	0.5	**100.0%**	79.7, 100.0%
CIN 2	2240	0	3779.8	0.0	2258	14	3794.8	0.4	**100.0%**	69.7, 100.0%
CIN 3	2240	0	3779.8	0.0	2258	8	3796.5	0.2	**100.0%**	41.2, 100.0%
AIS	2240	0	3779.8	0.0	2258	5	3796.3	0.1	**100.0%**	<0.0, 100.0%
Cervical Cancer	2240	0	3779.8	0.0	2258	0	3796.6	0.0	**N/A**	n/a

Source: Table 7-4, CSR 013v1, p. 242 and Table on p. 14 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

- The point estimates of vaccine efficacy in the different geographic regions were all 100%, although this did not reach statistical significance in the Asia-Pacific region (smaller number of subjects and cases). (Source: Table 11-59, CSR 013v1, p. 598, not shown here)

Efficacy Against HPV 6, 11, 16, 18 related CIN in the MITT-1 and MITT-2 Populations

- The point estimate of vaccine efficacy for HPV 6/11/16/18 related CIN in the MITT-1 population (which is like the PPE population but includes protocol violators) was also 100%. There were additional cases added to the placebo group but not to the Gardasil group.
- In the MITT-2 population, the subjects were naive to the relevant HPV type at Day 1, but cases were counted starting 30 days after the first dose. Again vaccine efficacy remains high against the composite endpoint (96.5%, 95% CI: 86.7, 99.6%) and also for the specific vaccine HPV type to which subjects are naïve. There were 20 additional cases of HPV 6, 11, 16, and/or 18 related CIN in placebo recipients as compared to the PPE population, but only 2 cases in the Gardasil recipients. (Source: Table 7-7. CSR 013v1, p. 249 and Table on p. 17 of Amendment 0015, submitted 3/22/06 for Protocol 013v1, not shown here.) (AN 24206) was seronegative and PCR negative for HPV 6 at baseline (with HSIL at Day 1 Pap testing) and developed CIN 1 associated with HPV 6 at 6 days following dose 2,. In addition, she was PCR positive for HPV 18 at baseline and developed CIN 1 associated with 18 also at the same time. (She is only counted as a case of HPV 6 CIN in the MITT-2 population because this was the HPV type to which she was naïve.) The second subject (AN 30205) developed CIN 1 associated with HPV 18 at 27 days following dose 3. However, even though this subject had been randomized to receive Gardasil and was given placebo by mistake, she was nonetheless counted as a vaccine case.

Efficacy Against HPV 6, 11, 16, 18 related CIN in MITT-3 Population

- In the MITT-3 population, the subjects did not have to be naïve to the relevant HPV type, and cases were counted starting 1 month after the first dose.
- 63 cases of HPV 6/11/16/18 related CIN were added to the Gardasil group and 56 additional cases were added to the placebo group when subjects are included regardless of baseline vaccine HPV serostatus and/or PCR status. For all HPV 6, 11, 16, 18 related CIN, the point estimate of efficacy in the MITT-3 population was 42.9% (95% CI: 28.9, 58.6%).
- The sponsor noted that all the additional cases occurred in subjects who were seropositive and/or PCR positive to the relevant HPV type at Day 1. Most of the cases added were HPV 16 related CIN (HPV 16 is the most common vaccine HPV type noted in the population overall). (See Table 92 below.)
- The point estimate for Gardasil efficacy against HPV 16 related CIN was lowest among the vaccine HPV types, and was thought by the sponsor to be due to the higher prevalence of HPV 16 in this population.
- The point estimate for vaccine efficacy against vaccine HPV type related CIN 2 or worse was again low (22.8%) without reaching statistical significance.

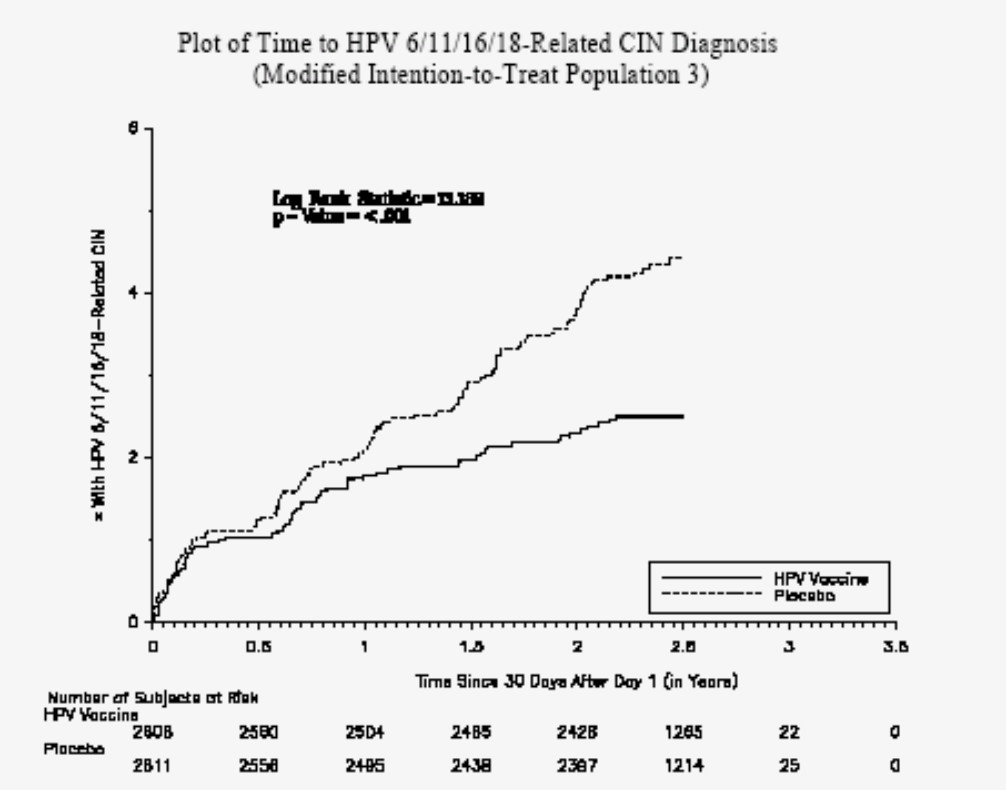
TABLE 92
Protocol 013: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN by HPV Type and Severity (MITT-3 Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related CIN	2607	65	5566.5	1.2	2611	113	5525.4	2.0	**42.9%**	21.9, 58.6%
By HPV Type										
HPV 6 Related CIN	2607	4	5593.5	0.1	2611	18	5570.6	0.3	**77.9%**	32.8, 94.6%
HPV 11 Related CIN	2607	0	5597.2	0.0	2611	9	5574.5	0.2	**100.0%**	49.5, 100.0%
HPV 16 Related CIN	2607	54	5577.4	1.0	2611	79	5551.6	1.4	**32.0%**	2.6, 52.8%
CIN 18 Related CIN	2607	8	5590.0	0.1	2611	22	5570.5	0.4	**63.8%**	15.5, 86.1%
By Lesion Type										
CIN 1	2607	41	5576.2	0.7	2611	83	5534.5	1.5	**51.0%**	27.9, 67.1%
CIN 2 or worse	2607	48	5585.0	0.9	2611	62	5570.4	1.1	**22.8%**	<0.0, 48.2%
CIN 2	2607	35	5590.4	0.6	2611	40	5573.7	0.7	**12.8%**	<0.0, 46.2%
CIN 3/AIS	2607	35	5588.8	0.6	2611	35	5579.0	0.6	**0.2%**	< 0.0, 39.3%
Cervical Cancer	2607	0	5597.2	0.0	2611	0	5582.5	0.0	**N/A**	N/A

Source: Table 7-8, CSR 013v1, p. 250

- Also shown is a time to event curve, which shows follow-up of subjects in the MITT-3 population through 2.5 years. Not all subjects had reached this timepoint at the time of submission of the BLA. The time to event curves were similar for the vaccine and placebo recipients through Month 6 after Day 1. However, the curves separate after this time point, and there is a suggestion of a higher risk of developing a case of HPV 6, 11, 16, and/or 18 in the placebo group compared to the vaccine group. As noted in Study 015, further follow-up is necessary before a definitive conclusion can be reached.

FIGURE 13
Protocol 013



Source: Figure 11-5, CSR 013v1, p. 600

Incidence Rates of Non-Vaccine HPV type Related CIN in the MITT-3 Population

TABLE 93
Protocol 013: Incidence of Non-Vaccine HPV Type Related CIN by Severity (MITT-3)

	Gardasil N=2717				Placebo N=2725			
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk (95% CI)	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk (95% CI)
Non-Vaccine HPV Type related CIN	2607	225	5452.7	4.1 (3.6, 4.7)	2611	241	5392.4	4.5 (3.9, 5.1)
CIN 1	2607	188	5467.5	3.4 (3.0, 4.0)	2611	216	5412.4	4.0 (3.5, 4.6)
CIN 2 or worse	2607	71	5579.6	1.3 (1.0, 1.6)	2611	58	5557.5	1.0 (0.8, 1.3)
CIN 2	2607	50	5587.9	0.9 (0.7, 1.2)	2611	48	5565.3	0.9 (0.6, 1.1)
CIN 3/AIS	2607	33	5589.0	0.6 (0.4, 0.8)	2611	25	5574.3	0.4 (0.3, 0.7)
Cervical cancer	2607	0	5597.2	0.0 (0.0, 0.1)	2611	0	5582.5	0.0 (0.0, 0.1)

Source: Table 7-11, CSR 013v1, p. 255

Reviewer's Comment: The above analysis is the MITT-3 population. There is a slightly lower incidence of CIN not related to vaccine type HPV in the Gardasil group (4.1) as compared to to the placebo group (4.5), although there is a slightly higher incidence of non-vaccine HPV related CIN 3/AIS in the Gardasil group (0.6) as compared to the placebo group (0.4). The results for the specific non-vaccine HPV types will not be available until sometime next year. See discussion in Study 005 and the overall efficacy section.

Potential Impact of Other Factors on Vaccine Efficacy

- **Reason for colposcopy:** The reason for colposcopy that led to a cervical biopsy did not impact the point estimate of vaccine efficacy. (Source: Table 7-10, p. 254; Tables 11-61 and 11-62, p. 601-2, CSR 013v1, not shown here)
- **Dropouts:** Cases were imputed among subjects lost to follow-up using the 2 methods previously described. The imputed VEs for the PPE population were consistent with the primary PPE results. (Source: Table 11-63, CSR 013v1, p. 603, not shown here)
- **Biopsies Outside the Context of the Study**: No subjects in the PPE population who had a diagnosis of CIN from a post-Month 7 biopsy performed outside the context of the study had a PCR result (positive or negative) for the relevant HPV type. The results for VE are identical to those of the primary PPE analysis. (Source: Text p. 241, CSR 013v1 and Table 11-64, CSR 013v1, p. 604, not shown here)

- **Lab Diagnosis:** When the central lab diagnosis was used to assess VE against HPV 6, 11, 16, or 18 related CIN or AIS, the VE was 100%, and the 95% CIs similar (93.3%, 100%) to those of the primary PPE analysis. (Source: Table 7-12, CSR 013v1, p. 259)

Efficacy Against HPV 16/18 Related CIN in the PPE Population

The point estimates for vaccine efficacy against HPV 16/18 related CIN were 100% (95% CI: 85.9, 100%) in the PPE. (See Table 94 below.)

TABLE 94
Protocol 013: Analysis of Efficacy Against HPV 16/18 Related CIN by HPV Type and Severity (PPE Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 16/18 Related CIN	2200	0	3716.7	0.0	2222	28	3732.0	0.8	**100.0%**	85.9, 100.0%
By HPV Type										
HPV 16 Related CIN	1887	0	3201.0	0.0	1847	22	3130.6	0.7	**100.0%**	82.1, 100.0%
CIN 18 Related CIN	2101	0	3557.9	0.0	2120	8	3569.1	0.2	**100.0%**	41.2, 100.0%
By Lesion Type										
CIN 1	2200	0	3716.7	0.0	2222	17	3734.2	0.5	**100.0%**	75.7, 100.0%
CIN 2 or worse	2200	0	3716.7	0.0	2222	19	3736.0	0.5	**100.0%**	78.5, 100.0%
CIN 2	2200	0	3716.7	0.0	2222	13	3736.5	0.3	**100.0%**	67.0, 100.0%
CIN 3	2200	0	3716.7	0.0	2222	8	3738.1	0.2	**100.0%**	41.1, 100.0%
AIS	2200	0	3716.7	0.0	2222	5	3737.9	0.1	**100.0%**	<0.0, 100.0%
Cervical Cancer	2200`	0	3716.7	0.0	2222	0	3738.2	0.0	**NA**	NA

From Table 7-13, CSR 013v1, p. 261 and Table on p. 15 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

Efficacy Against HPV 16/18 related CIN in the MITT-3 Population

- In the MITT-3 population, the VE against HPV 16/18 related CIN was 33.7% [95% CI: 7.5, 52.7%]. The efficacy against HPV 16 related CIN was 32.0% [95% CI: 2.6, 52.8%] compared to 63.8% [95% CI: 15.5, 86.1%]). for HPV 18 related CIN. (Source: Tables 11-70, CSR 013v1, p. 610, not shown here)

Analyses of Vaccine Efficacy Against HPV 6, 11, 16, or 18 Related External Genital Lesions

Efficacy Against HPV 6, 11, 16, and/or 18 related EGLs in the PPE Population

This was the second co-primary endpoint for Study 013. The pointe estimate of efficacy against HPV 6, 11, 16, and/or 18 related EGLs was 100% (95% CI: 88.4, 100%). This was seen for all vaccine HPV types and for the low grade and high grade lesions noted in the Table 95 below.

TABLE 95
Protocol 013: Analysis of Efficacy Against HPV 6/11/16/ 18 Related EGLs by HPV type and Severity (PPE Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related EGL	2261	0	3865.2	0.0	2279	40	3868.4	1.0	**100.0%**	88.4, 100.0%
By HPV Type										
HPV 6 Related EGL	1978	0	3378.7	0.0	1991	23	3391.1	0.7	**100.0%**	82.5, 100.0%
HPV 11 Related EGL	1978	0	3378.7	0.0	1991	10	3399.0	0.3	**100.0%**	55.1, 100.0%
HPV 16 Related EGL	1890	0	3232.7	0.0	1855	10	3166.6	0.3	**100.0%**	56.3, 100.0%
CIN 18 Related EGL	2120	0	3627.5	0.0	2136	3	3647.8	0.1	**100.0%**	< 0.0, 100.0%
By Lesion Type										
Condyloma, VIN 1, VaIN 1	2261	0	3865.2	0.0	2279	34	3870.7	0.9	**100.0%**	88.5, 100.0%
VIN 2/3 or VaIN 2/3	2261	0	3865.2	0.0	2279	7	3887.5	0.2	**100.0%**	30.2, 100.0%
Vulvar or vaginal cancer	2261	0	3865.2	0.0	2279	0	3890.7	0.0	**NA**	NA

From Table 7-14, CSR 013, p. 264

Efficacy Against HPV 6, 11, 16, or 18 related EGLs in the MITT-2 Population

- In the MITT-2 population, where the subjects were naive to the relevant HPV type at Day 1, and cases were counted starting 30 days after the first dose, the point estimate for efficacy was 94.9% (95% CI: 84.4, 99.0%). The sponsor provides descriptions of the 3 vaccinees who developed a case. (Source: Table 7-17, CSR 013v1, p. 270, not shown here) Descriptions of the subjects who developed a case in this population are provided below.
  - **AN 31045:** This subject, who was seropositive to HPV 16 at baseline, developed an HPV 6-related condyloma and an HPV 6-related VIN 1 lesion 21 days after the Month 7 visit. She had a good immune response to all vaccine HPV types after 3 doses of vaccine.

- **AN 33405:** This subject developed an HPV 6-related condyloma 1 day after the Month 12 visit. She received all 3 vaccine doses. HPV 6 infection was first detected by PCR testing at the Month 3 visit, and remained positive at the Month 7 visit. At the Month 7 visit, the Pap test revealed "atypical squamous cells of undetermined significance (ASCUS), favor reactive". The Month 12 Pap test revealed ASC-US, and reflex HPV testing was reportedly high-risk probe positive and low risk probe negative. She developed a good immune response to vaccination.
- **AN 24533:** This subject developed an HPV 11-related condyloma diagnosed by external genital biopsy 3 months after the Month 18 visit. The subject became pregnant after the vaccination series, approximately 9 months Postdose 3. She experienced a fetal loss at 4 weeks gestational age. Pap testing was negative at enrollment, and at Month 7, Month 12, and at an unscheduled visit post-Month 18. At enrollment, genital HPV PCR testing was negative for HPV 6, 11, 16, and 18. At the Month 3 visit, the swab was not adequate for HPV 11 PCR testing. HPV 11 infection was first detected by PCR testing at the Month 7 visit. The subject underwent cervical and vaginal biopsy following colposcopy at 3 months after Month 18. The cervical biopsy was negative by histology, although it was HPV 11 positive by PCR testing. The vaginal biopsy revealed HPV 11-related condyloma and VaIN 1. External genital lesion biopsies conducted at subsequent visits yielded HPV 11-related VIN 1 and HPV 11-related condyloma. She had a good immune response after 3 doses.

Efficacy Against HPV 6, 11, 16, or 18 related EGLs in the MITT-3 Population

- In the MITT-3 population (subjects included regardless of baseline serostatus and/or PCR status), the sponsor reported that the additional cases in each group occurred in subjects who were seropositive or PCR positive at Day 1.
- As the population is expanded to include subjects regardless of baseline sero- and/or PCR status at baseline (from the MITT-2 population to the MITT-3 population), 23 cases of HPV 6, 11, 16, and/or 18 related EGLs are added to the Gardasil group and 21 cases are added to the placebo group.
- The point estimate of vaccine efficacy against HPV 6, 11, 16, and/or 18 related EGLs is higher (67.8%, 95% CI: 49.3, 80.1%) than the point estimate of efficacy against vaccine type related CIN noted earlier in this review.
  Reviewer's Comment: This may be be due to lower prevalence of external genital lesions at Day 1 and perhaps to a shorter period of time to development of the vaccine HPV related external genital lesions.

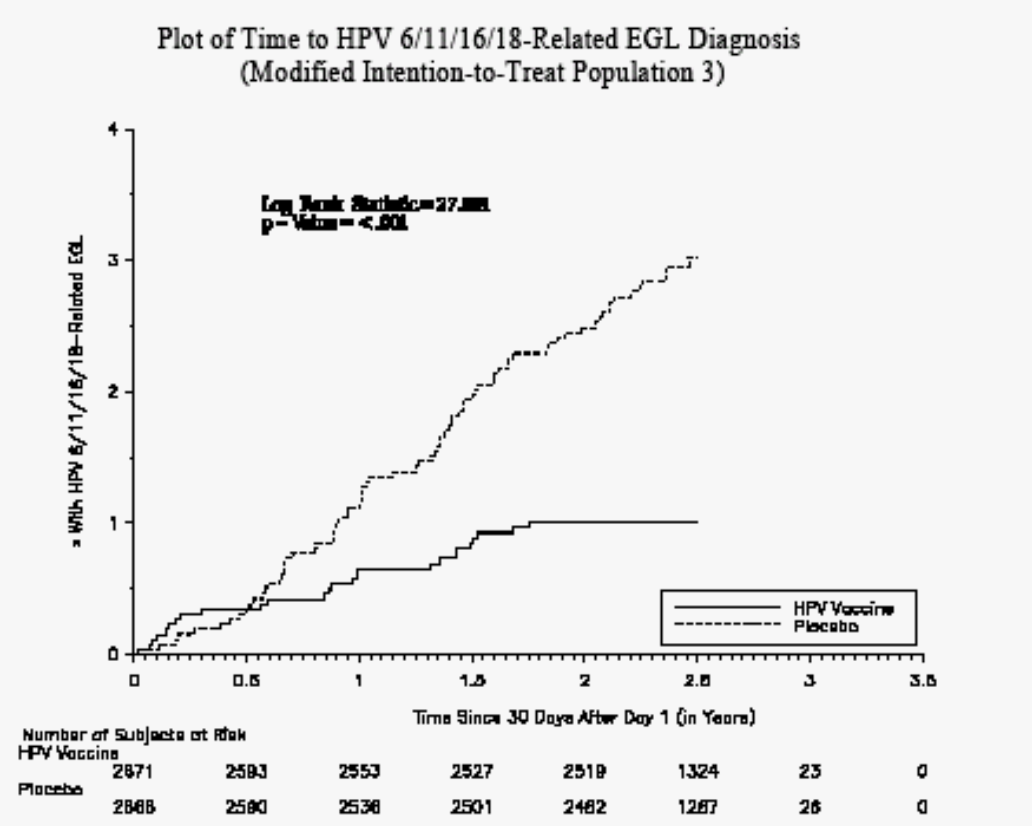
TABLE 96
Protocol 013: Analysis of Efficacy Against HPV 6, 11, 16, 18 related EGLs by HPV Type and Severity (MITT-3 Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related EGL	2671	26	5697.6	0.5	2668	80	5648.4	1.4	**67.8%**	49.3, 80.1%
By HPV Type										
HPV 6 Related EGL	2671	19	5707.2	0.3	2668	51	5673.4	0.9	**63.0%**	36.2, 79.4%
HPV 11 Related EGL	2671	2	5728.0	0.0	2668	16	5708.2	0.3	**87.5%**	47.0, 98.6%
HPV 16 Related EGL	2671	5	5724.6	0.1	2668	19	5708.5	0.3	**73.8%**	27.3, 92.3%
HPV 18 Related EGL	2671	1	5728.9	0.0	2668	8	5713.2	0.1	**87.5%**	7.0, 99.7%
By Lesion Type										
Condyloma, VIN 1, VaIN 1	2671	22	5701.8	0.4	2668	72	5653.1	1.3	**69.7%**	50.6, 82.1%
VIN 2/3 or VaIN 2/3	2671	4	5726.9	0.1	2668	11	5715.5	0.2	**63.7%**	< 0.0, 91.6%
Vulvar or vaginal cancer	2671	0	5731.1	0.0	2668	0	5721.1	0.0	**NA**	NA

From Table 7-18, CSR 013v1, p. 271

- The sponsor also presents the time to event in Figure 14 for the MITT-3 population. The time to event curve is displayed through app. 2.5 years of follow-up. The curves were identical through Month 6; after that time point, there is suggestion that the risk developing HPV 6, 11, 16 and/or 18 related EGL was lower in Gardasil recipients as compared to placebo recipients. As in earlier time to event curves, not all subjects had reached the 2.5 year time point, and further follow-up is necessary before a definitive conclusion can be reached.

FIGURE 14
Protocol 013



From Figure 11-6, CSR 013v1, p. 617

Potential Impact of Missing Data on estimate of Efficacy Against Vaccine HPV Type Related CIN or AIS

- **Dropouts:** The imputed VE for the PPE population and MITT-2 population were consistent with the primary PPE results regardless of the method used. (Source: Table 11-74, CSR 013v1, p. 618, not shown here)
- **Biopsies Outside the Context of the Study:** No subjects in the PPE population who were not already cases of HPV 6-, HPV 11-, HPV 16-, or HPV 18-related EGLs in the primary analysis had a post Month 7 outside study biopsy with a diagnosis of EGL.

Efficacy Against HPV 6, 11, 16, 18 related cervical disease and EGL
Efficacy Against HPV 6, 11, 16, or 18 related CV and EGLs in the PPE Population

- In the PPE population, the VE was 100% (95% CI: 94.6, 100%) for all types of vaccine related HPV CV and EGL disease. (See Table 97 below). The results of the MITT-2 and MITT-4 analyses are consistent with that in the PPE population. (Additional sources: Tables 11-77, 11-78, CSR 013v1, p. 621-2, not shown here)

TABLE 97
Protocol 013: Analysis of Efficacy Against HPV 6/11/16/18 related CV and EGL Disease by HPV Type (PPE Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related Disease	2263	0	3884.0	0.0	2279	70	3873.5	1.8	**100.0%**	94.6, 100.0%
HPV 6 Related Disease	1980	0	3395.5	0.0	1991	26	3407.2	0.8	**100.0%**	84.7, 100.0%
HPV 11 Related Disease	1980	0	3395.5	0.0	1991	12	3415.4	0.4	**100.0%**	63.8, 100.0%
HPV 16 Related Disease	1892	0	3247.4	0.0	1855	30	3171.5	0.9	**100.0%**	87.2, 100.0%
HPV 18 Related Disease	2121	0	3644.7	0.0	2136	10	3664.6	0.3	**100.0%**	55.1, 100.0%

Source: Table 11-76, CSR 013v1, p. 6120

Efficacy Against HPV 6, 11, 16, or 18 related CV and EGL Disease in the MITT-3 Population

In the MITT-3 population, the point estimate for efficacy against HPV 6, 11, 16 and/or 18 related CV and EGL combined is 50.4% (95% CI: 35.4, 62.1%). (See Table 98 below.)

TABLE 98
Protocol 013: Analysis of Efficacy Against HPV 6/11/16/18 related CV and EGL Disease by HPV Type (MITT-3 population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related Disease	2673	87	5630.8	1.5	2672	173	5558.8	3.1	**50.4%**	35.4, 62.1%
HPV 6 Related Disease	2673	22	5725.9	0.4	2672	62	5685.1	1.1	**64.8%**	41.9, 79.4%
HPV 11 Related Disease	2673	2	5750.8	0.0	2672	21	5728.6	0.4	**90.5%**	61.2, 98.9%
HPV 16 Related Disease	2673	58	5670.2	1.0	2672	91	5641.8	1.6	**36.6%**	10.9, 55.2%
HPV 18 Related Disease	2673	9	5739.5	0.2	2672	28	5718.6	0.5	**68.0%**	30.2, 86.7%

From Table 11-79, CSR 013v1, p. 623

- The sponsor reports that through the 2-year postenrollment follow-up, the cumulative incidence in the placebo group of vaccine HPV type related disease was 6.8% for placebo recipients and 3.3% in the vaccine group. For disease overall, even in the MITT-3 population, the risk of developing vaccine HPV type related disease was reduced from 1 in 15 subjects to 1 in 31 subjects (Sponsor calculations).

Incidence of HPV 16 related CIN and EGL in Recipients of the Monovalent HPV 16 vaccine

- In Protocol 013, 304 subjects were randomized to receive monovalent HPV 16 vaccine in the context of Protocol 012 (the monovalent HPV 16 bridging substudy of Protocol 013). These subjects were not included in the evaluation of efficacy of the quadrivalent HPV vaccine. None of these subjects in the PPE, MITT-1, MITT-2, and MITT-4 populations developed HPV 16-related CIN or HPV 16-related EGL. In the MITT-3 population, 6 subjects developed HPV 16-related CIN and 2 subjects developed HPV 16-related EGL. These subjects in the MITT-3 population were seropositive and/or PCR positive to HPV 16 prior to their Day 1 vaccination.

Exploratory Analyses Against ALL CV and EGL Disease

Exploratory Efficacy Against ALL CIN in the RMITT-2

- The RMITT-2 population is naïve to 4 types, has a normal Pap at Day 1, and cases were counted starting 1 month after dose 1. The point estimate for vaccine efficacy against all CIN irrespective of HPV type was relatively low at 24.9% (95% CI: 2.2, 42.5%). The point estimate for efficacy was higher for all CIN 2 or worse (39.4%) but did not reach statistical significance. (See Table 99 below.)

TABLE 99
Protocol 013: Analysis of Efficacy Against All CIN Irrespective of HPV Type by Severity (RMITT-2 Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
CIN Due to Any HPV Type	1683	102	3635.8	2.8	1697	135	3613.1	3.7	**24.9%**	2.2, 42.5%
CIN 1	1683	90	3639.4	2.5	1697	117	3624.2	3.2	**23.4%**	<0.0, 42.5%
CIN 2 or worse	1683	26	3681.7	0.7	1697	43	3690.3	1.2	**39.4%**	<0.0, 64.2%
CIN 2	1683	19	3682.5	0.5	1697	31	3692.1	0.8	**38.5%**	<0.0, 67.2%
CIN 3	1683	10	3684.9	0.3	1697	21	3703.0	0.6	**52.1%**	< 0.0, 79.9%
AIS	1683	0	3685.7	0.0	1697	3	3704.5	0.1	**100.0%**	<0.0, 100.0%
Cervical cancer	1683	0	3685.7	0.0	1697	0	3704.8	0.0	**NA**	NA

Source: Table 7-21, CSR 013v1, p. 281 and Table on p. 20 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

Exploratory Efficacy Against ALL CIN in the MITT-3 Population

- The point estimate against CIN irresepective of HPV type was low (16.6%, 95% CI: 1.8, 29.1%). (See Table 100 below.)

TABLE 100
Protocol 013: Analysis of Efficacy Against CIN Irrespective of HPV Type by Severity (MITT-3 population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
CIN Due to Any HPV Type	2607	278	5424.1	5.1	2611	328	5339.1	6.1	**16.6%**	(1.8, 29.1%)
CIN 1	2607	223	5448.2	4.1	2611	282	5367.8	5.3	**22.1%**	(6.8, 34.9%)
CIN 2 or worse	2607	116	5567.4	2.1	2611	118	5545.3	2.1	**2.1%**	(<0.0, 24.9%)
CIN 2	2607	85	5581.1	1.5	2611	89	5556.0	1.6	**4.9%**	<0.0, 30.2%
CIN 3	**2607**	**65**	**5580.5**	**1.2**	**2611**	**56**	**5570.7**	**1.0**	**<0.0%**	**<0.0, 20.2%**
AIS	2607	1	5597.2	0.0	2611	5	5582.2	0.1	**80.1%**	<0.0, 99.6%
Cervical cancer	2607	0	5597.2	0.0	2611	0	5582.2	0.0	**NA**	NA

Source: Table 11-81, CSR 013v1, p. 623 and Table on p. 21 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

Reviewer's Comment: There was a slight increased incidence rate of CIN 3 due to any HPV type in the MITT-3 population. This was analyzed in the combined analysis from the 4 studies. See overall efficacy.

Exploratory Analyses of VE Against All HPV Related EGL in the RMITT-2 Population

- In the restricted MITT-2 population, the incidence of all EGLs in vaccinees was decreased compared to the incidence in placebo recipients. The point estimate of efficacy in subjects naïve to all 4 vaccine HPV types with a normal Pap test at Day 1 was 48.5% (95% CI: 21.5, 66.8%). (See Table 101 below).

TABLE 101
Protocol 013: Analysis of Efficacy Against EGL Irrespective of HPV Type by Severity (Restricted MITT-2 population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
EGL due to any HPV type	1726	35	3683.3	1.0	1733	68	3685.1	1.8	**48.5%**	21.5, 66.8%
Condyloma, VIN 1, VaIN 1	1726	31	3684.8	0.8	1733	64	3686.5	1.7	**51.5%**	24.5, 69.5%
VIN 2/3 or VaIN 2/3	1726	3	3708.0	0.1	1733	10	3728.3	0.3	**69.8%**	<0.0, 94.7%
Vulvar or vaginal cancer	**1726**	**1**	**3709.5**	**0.03**	**1733**	**0**	**3732.1**	**0.0**	**NA**	**NA**

Source: Table 7-22, CSR 013v1, p. 284

- There was one Gardasil recipients who developed anogenital cancer due to **not associated** with a vaccine HPV type. This subject, **AN 33082**, is a 20 year old female who had a negative Pap test at enrollment and was negative for evidence of prior exposure to HPV 6, 11, 16, and 18. She reported sexual debut at age 17, 1 lifetime partner, and use of injectable hormonal contraceptives. She switched to hormonal patch contraceptives after enrollment. She received all 3 doses of vaccine. Her Pap test was negative at Day 1, Month 7, Month 12, Month 18 and Month 24. Genital specimens obtained at Day 1, Month 3 and Month 7 were negative for HPV 6, 11, 16, and 18. Her pelvic and external genital exams were negative at enrollment, Month 7, Month 12 and Month 24. She developed a perineal lesion at Month 24 (posterior introitus). An external genital biopsy done 28 days after the Month 24 visit was positive for anogenital cancer, negative for the vaccine types. Her immune response to the vaccine HPV types was robust.

Exploratory Analyses of VE Against All HPV Related EGL in the MITT-3 Population

- In the MITT-3 population, there was an overall decrease in the incidence of all EGLs in the vaccine group compared to the incidence in placebo recipients, with a point estimate of efficacy of 31.5% (95% CI: 9.2, 48.5%). (See Table 102 below.)

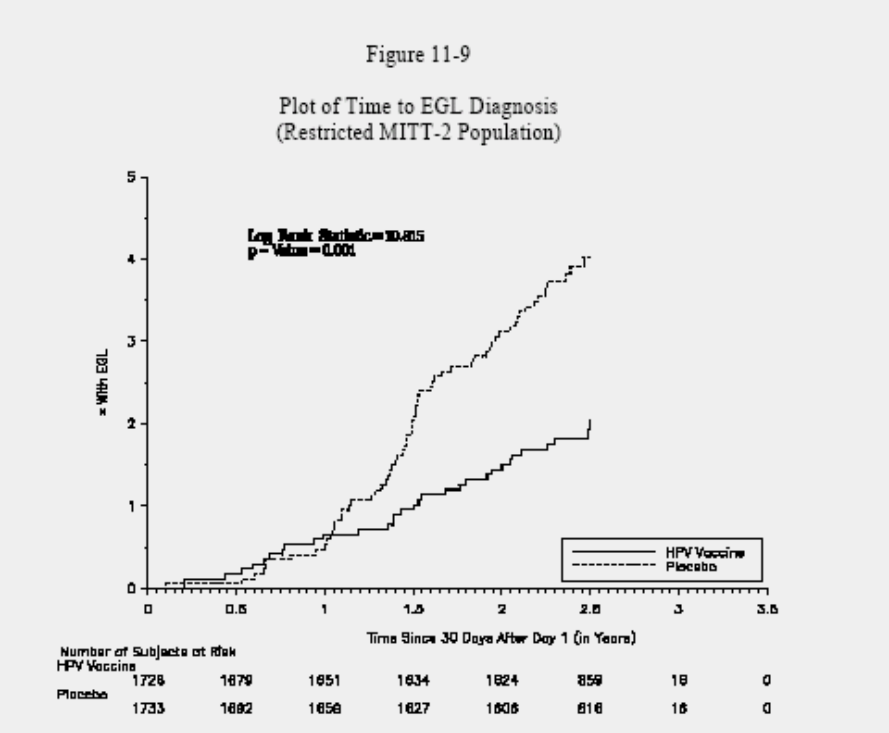
TABLE 102
Protocol 013: Analysis of Efficacy Against EGL Irrespective of HPV Type by Severity (MITT-3 population)

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
EGL due to any HPV type	2671	87	5641.9	1.5	2668	126	5598.5	2.3	**31.5%**	9.2, 48.5%
Condyloma, VIN 1, VaIN 1	2671	77	5647.6	1.4	2668	118	5605.4	2.1	**35.2%**	13.0, 52%
VIN 2/3 or VaIN 2/3	2671	12	5722.8	0.2	2668	18	5708.8	0.3	**33.5%**	<0.0, 70.8%
Vulvar or vaginal cancer	**2671**	**1**	**5731.1**	**0.02**	**2668**	**0**	**5721.1**	**0.0**	**NA**	**NA**

Source: Table 11-82, CSR 013v1, p. 628

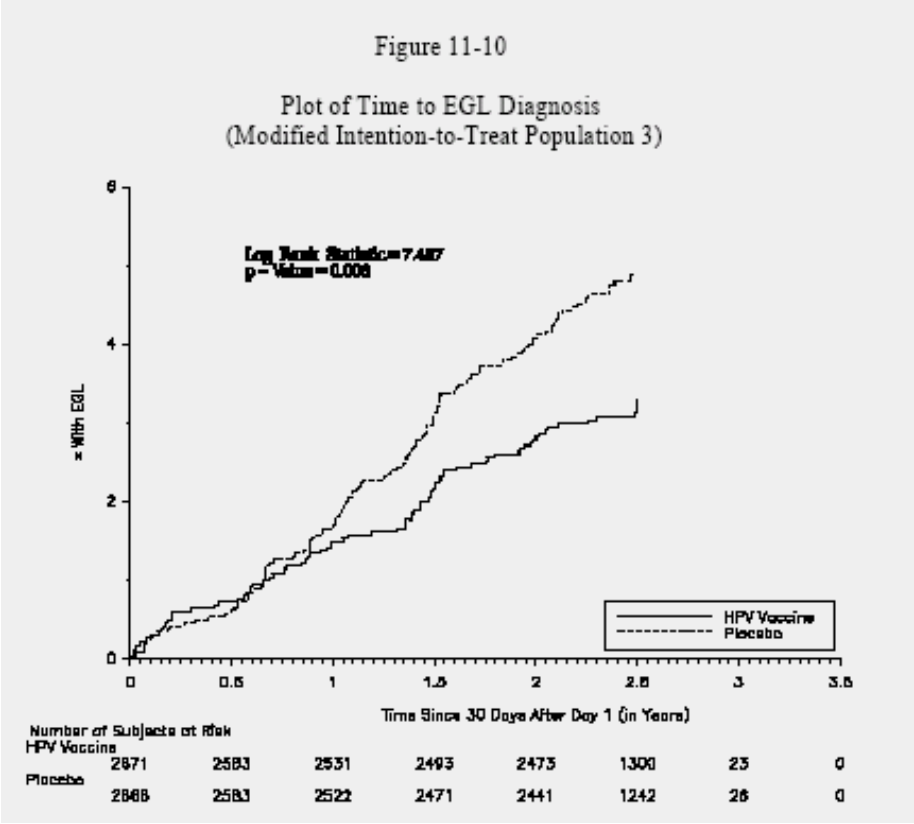
- The sponsor also presents time to event curves for the EGL diagnoses in the 2 populations above: RMITT-2 population and in the MITT-3 population. There was noted a suggestion of decreased risk of developing EGL irrespective of HPV type in Gardasil recipients as compared to placebo recipients. As noted earlier, further follow-up is necessary before a definitive conclusion can be reached.

FIGURE 15
Protocol 013



Source: Figure 11-9, CSR 013v1, p. 629

FIGURE 16
Protocol 013



Source: Figure 11-10, CSR 013v1, p. 630

- The cumulative incidences of HPV related disease in the placebo group in the RMITT-2 and MITT-3 population were 10.4% and 15.0%, respectively, over the duration of the follow-up, and in the vaccinees were 7.2% and 12.5%.

Exploratory Analysis of Efficacy Against All EGLs (Per Protocol Approach)

- A prespecified exploratory analysis of VE against all EGLs was performed in subjects who received all 3 vaccinations and were not general protocol violators. These subjects were negative for the vaccine HPV types and had a negative Pap test at Day 1 through Month 7. In this analysis, **prevalent disease related to vaccine HPV types is excluded**, and are reported to reflect the burden of prevalent and incident non-vaccine HPV related EGL disease. The results are shown Table 103 below. The results were reported to be homogeneous across the 4 geographic regions.

TABLE 103
Protocol 013: Secondary Analysis of Efficacy Against EGL Irrespective of HPV Type by Severity (Per Protocol Approach)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
EGL due to any HPV type	2380	25	4041.2	0.6	2390	66	4023.4	1.6	**62.3%**	39.4, 77.2%
Condyloma, VIN 1, VaIN 1	2380	23	4042.2	0.6	2390	60	4025.3	1.5	**61.8%**	37.3, 77.5%
VIN 2/3 or VaIN 2/3	2380	2	4051.9	0.0	2390	11	4057.6	0.3	**81.8%**	16.6, 98.0%
Vulvar or vaginal cancer	**2380**	**1**	**4053.2**	**0.02**	**2390**	**0**	**4061.9**	**0.0**	**NA**	**NA**

Source: Table 7-23, CSR 013v1, p. 287
Includes subjects who were not general protocol violators and received all 3 vaccinations. Subjects were required to be seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s) when assessing disease due to vaccine HPV types and were required to have a Pap test diagnosis of "Negative for SIL" Day 1 through Month 7 when assessing all other disease. Cases were counted starting after Month 7.

Reviewer's Comment: This analysis excluded subjects with prevalent disease to vaccine HPV types through Month 7. When results of this analysis are compared to the primary analysis for VE against vaccine related EGLs in the PPE population, there were an additional 25 cases in the vaccine group and an additional 26 cases in the placebo group. The majority of these cases were low grade in nature. There were 4 additional cases of VIN 2/3 or VaIN 2/3 in the placebo group and 2 additional cases in the vaccine group, and there was 1 additional case of cancer in the vaccine group and none in the placebo group.

Exporatory Analysis of Efficacy against Vaccine versus Non-Vaccine HPV Type Related disease

Efficacy Against Non-Vaccine HPV related CIN in the RMITT-2 Population

- As shown in Table 104 below, the incidence of CIN not related to non-vaccine HPV types was comparable in the vaccine (2.8) and placebo (2.9) groups.

TABLE 104
Protocol 013: Exploratory Analysis of Potential Replacement of Vaccine HPV Types in CIN (Restricted MITT-2 Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
CIN Due to Any HPV type	1683	102	3635.8	2.8	1697	135	3613.1	3.7	**24.9%**	2.2, 42.5%
Related to HPV 6/11/16/18	1683	0	3685.7	0.0	1697	39	3689.9	1.1	**100.0%**	90.1, 100.0%
Not Related to HPV 6/11/16/18	1683	102	3635.8	2.8	1697	107	3627.2	2.9	**4.9%**	<0.0, 28.2%

Source: Table 7-24, CSR 013v1, p. 290

Efficacy Against Vaccine and Non-Vaccine HPV related EGL in the RMITT-2 Population

- Again, the incidence of cases of non-vaccine HPV types is comparable between the Gardasil group (0.9) and the placebo group (0.9) in the RMITT-2 population. (See Table 105 below.)

TABLE 105
Protocol 013: Exploratory Analysis of Potential Replacement of Vaccine HPV Types in EGL (Restricted MITT-2 Population)

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
EGL Due to Any HPV type	1726	35	3683.3	1.0	1733	68	3685.1	1.8	**48.5%**	21.5, 66.8%
Related to HPV 6/11/16/18	1726	2	3707.8	0.1	1733	39	3707.4	1.1	**94.9%**	80.2, 99.4%
Not Related to HPV 6/11/16/18	1726	33	3685.0	0.9	1733	35	3707.8	0.9	**5.1%**	<0.0, 42.9%

Table 7-25, CSR 013v1, p. 291

Exploratory Analysis of VE with Respect to Clinically Diagnosed EGLs in RMITT-2 and MITT-3 Populations

- The clinical impression of a lesion rendered by a study investigator during an EGL examination was used as an endpoint for this analysis, and conducted in the RMITT-2 and MITT-3 populations.
- In the RMITT-2 population, the point estimate of vaccine efficacy of Gardasil against clinically diagnosed EGLs was modest, but without statistical significance (VE = 28.0% [95% CI:.<0.0, 51.4%]). (Source: Table 7-26, CSR 013v1, p. 293, not shown here)
- In the MITT-3 population, the point estmate of efficacy against clinically diagnosed EGLs (12.3%, 95% CI: <0.0, 33.0%). was lower as compared to the RMITT-2 population, again not reaching statistical significance. (Source: Table 11-85, CSR 013v1, p. 633, not shown here)

Exploratory Analysis of Efficacy in Subjects with Evidence of Prior vaccine HPV type infection (i.e., seropositive and/or PCR positive)
Exploratory Analysis of Efficacy in subjects who were seropositive <u>and/or</u> PCR positive for vaccine HPV type related CIN

- In Protocol 013, in subjects who were non-naïve (i.e., seropositive and/or PCR positive for the relevant HPV type at Day 1), the incidence rate for HPV 6, 11, 16, 18 related CIN the Gardasil group (4.7) was higher than that seen for the placebo group (4.4), with a point estimate of efficacy of -6.8% [95% CI: <0.0, 26.3%], although the difference did not reach statistical significance. (See Table 106 below.)

TABLE 106
Protocol 013: Analysis of Efficacy Against Vaccine HPV Type Related CIN Among Subjects who were PCR Positive and/or Seropositive for the Relevant Vaccine HPV Type at Day 1

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	685	64	1367.9	4.7	664	58	1324.0	4.4	-6.8%	(<0.0, 26.3%)
CIN 2 or worse	685	48	1385.3	3.5	664	35	1350.3	2.6	-33.7%	(<0.0, 15.3%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0019, Efficacy Information Amendment, submitted 4/7/06 in response to CBER comments, Table 1e-2, p. 13

Exploratory Analysis of Efficacy in subjects who were seropositive and PCR negative for vaccine HPV type related CIN

- In subjects who were **PCR negative and seropositive** for the relevant vaccine HPV type at Day 1, the point estimate for vaccine efficacy against HPV 6, 11, 16, 18 related CIN was 100% (95% CI: <0.0, 100%), but the number of cases in the placebo group was small (2 cases of HPV 16 related CIN 1), and the efficacy did not reach statistical significance. (See Table 107 below.)

TABLE 107
Protocol 013: Analysis of Efficacy Against HPV 6/11/16/18 related CIN or Worse Among Subjects who were PCR Negative and Seropositive for the Relevant Vaccine HPV Type(s) at Day 1

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person-years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	377	0	806.1	0.0	379	2	800.9	0.2	100.0%	(<0.0, 100%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0019, Efficacy Information Amendment, submitted 4/7/06 in response to CBER comments, Table 1d-1, p. 8

Exploratory Analysis of Efficacy in subjects who were seronegative and PCR positive for vaccine HPV type related CIN

- In subjects who were **PCR positive and seronegative** for a vaccine HPV types (**consistent with early infection), t**he point estimate of efficacy against HPV 6, 11, 16, 18 related CIN was 20.4% (95% CI: <0.0, 54.8%) and is without statistical significance). The point estimate of efficacy against CIN 2 or worse is low (12.6%, 95% CI: <0.0, 57.7%) and does not reach statistical significance. (See Table 108 below.)

TABLE 108
Protocol 013: Analysis of Efficacy Against Vaccine HPV Type Related CIN Among Subjects who were PCR Positive and Seronegative for the Relevant Vaccine HPV Type at Day 1

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Percent Reduction	95% CI
HPV 6/11/16/18 related CIN	232	26	447.9	5.8	213	30	411.1	7.3	20.4%	<0.0, 54.8%
CIN 2 or worse	232	17	458.0	3.7	213	18	423.7	4.2	12.6%	<0.0, 57.7%

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 7-29, CSR 013v1, p. 301 and Table on p. 22 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

Exploratory Analysis of Efficacy in subjects who were seronegative and PCR positive for HPV 16/18 related CIN

In subjects who were **PCR positive and seronegative (HPV 16 or 18)**, the incidence of HPV 16/18 related CIN 2/3 or worse was slightly lower in Gardasil recipients (4.9) as compared to the placebo group (5.5), but the point estimate of efficacy was 12.0% and did not reach statistical signifcance (see Table 109 below).

TABLE 109

Protocol 013: Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse Among Subjects Who Were PCR Positive and Seronegative for the Relevant Vaccine HPV Types

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
HPV 16/18 related CIN 2/3 or worse	180	17	348.9	4.9	158	17	307.2	5.5	**12.0%**	<0.0, 57.7%

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 7-30, CSR 013v1, p. 302

Exploratory Analysis of Efficacy in subjects who were seropositive and PCR positive for vaccine HPV type related CIN

- In subjects who were **seropositive and PCR positive at baseline, t**he point estimate of vaccine efficacy for this endpoint was below zero (-12.5%), but did not reach statistical significance. (See Table 110 below).

TABLE 110

Protocol 013: Analysis of Efficacy Against Vaccine HPV Type Related CIN Among Subjects who were PCR Positive and Seropositive for the Relevant Vaccine HPV Type at Day 1

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years 4.4at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Percent Reduction	95% CI
HPV 6/11/16/18 related CIN	156	38	271.5	14.0	137	29	233.0	12.4	-12.5%	<0.0, 32.4%
CIN 2 or worse	156	31	278.9	11.1	137	19	247.1	7.7	-44.6%	<0.0, 20.9%

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 11-88, CSR 013v1, p. 636 Table on p. 24 of Amendment 0015, submitted 3/22/06 for Protocol 013v1.

Reviewer Comment: ---------- There are admitted difficulties with such subgroup analyses. For example, the resulting subgroup for each treatment arm may not have comparable baseline characteristics. Thus, CBER requested additional information on the baseline characteristics in each treatment group for subjects who were PCR (+) and sero (+) and who developed CIN 2/3 or worse due to the respective HPV type. In Protocol 013, the subjects who received Gardasil in those seropositive and PCR positive to at least one vaccine HPV type had a higher baseline incidence of HSIL (6.5%) as compared to the placebo recipients (3.7%). It is possible that this contributed to the higher incidence of

cases in the vaccine group as compared to the placebo group. In a logistic regression analysis performed by the sponsor, baseline Pap test was a factor predictive of development of CIN 2 or worse. This analysis was requested across studies 007, 013, and 015. A full discussion of this subgroup and analyses are located in the conclusions for Study 013 and in the Overall Efficacy Summary.

Exploratory Efficacy in subjects who were seropositive and/or PCR positive for vaccine HPV type related EGL

Exploratory Analysis of Efficacy in subjects who were seronegative and PCR positive for vaccine HPV type related EGLs

- In an exploratory analysis of efficacy against **vaccine HPV type related EGLs** among subjects who were **PCR positive and seronegative** for the relevant HPV type at Day 1, the overall incidence rates for HPV 6, 11, 16, 18 related EGL was the same in the Gardasil group (3.6) and the placebo group (3.6), and the point estinate of efficacy was 0.9% (95% CI: <0.0, 52.9%). There was no evidence that the vaccine prevented vaccine HPV type related EGLs in these subjects.

TABLE 111

Protocol 013: Analysis of Efficacy Against Vaccine Type HPV Related EGLs Among Subject who were PCR Positive and Seronegative for the Relevant Vaccine HPV Type at Day 1

	Gardasil N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6/11/16/18 Related EGL	238	17	477.8	3.6	221	16	445.5	3.6	**0.9%**	<0.0, 52.9%
By Lesion Type										
Condyloma, VIN 1, VaIN 1	238	14	481.6	2.9	221	15	446.9	3.4	**13.4%**	<0.0, 61.3%
VIN 2/3 or VaIN 2/3	**238**	**3**	**497.6**	**0.6**	**221**	**1**	**467.2**	**0.2**	**-181.7%**	**<0.0, 77.4%**
Vulvar or vaginal cancer	238	0	501.3	0.0	221	0	468.6	0.0	**NA**	NA

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least one injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 7-31, CSR 013v1, p. 303

Exploratory Analysis of Efficacy in subjects who were seropositive and PCR negative for vaccine HPV type related EGLs

- In subjects who were **PCR negative and seropositive** at Day 1 for the relevant HPV type, there were no cases of vaccine type HPV related EGLs were noted in either the vaccine or placebo group.

Exploratory Analysis of Efficacy in subjects who were seropositive and PCR positive for vaccine HPV type related EGLs

- In the **seropositive and PCR positive** subgroup, there was a somewhat higher incidence of EGLs in the placebo group (2.5) compared with the Gardasil group (2.1) for vaccine HPV type related EGLs, with a vaccine efficacy estimate that did not reach statistical significance (14.2%, 95% CI: <0.0, 74.3%). (See Table 112 below).

Reviewer's Comment: There is 1 case of HPV 18 related EGL in a subject who had this chronic infection in the Gardasil group and none in the placebo group.

TABLE 112
Protocol 013: Analysis of Efficacy Against Vaccine HPV Related EGLs Among Subjects who were PCR Positive and Seropositive for the Relevant HPV Type at Day 1

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=2717				Placebo N=2725					
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person-years 4.4at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
HPV 6/11/16/18 related EGL	158	7	330.3	2.1	142	7	283.3	2.5	**14.2%**	<0.0, 74.3%
By Lesion Type										
Condylona, VIN 1 or VaIN 1	158	6	330.7	1.8	142	6	284.4	2.1	**14.0%**	<0.0, 77.0%
VIN 2/3 or VaIN 2/3	158	1	338.9	0.3	142	1	291.0	0.3	**14.1%**	<0.0, 98.9%
Vulvar or Vaginal Cancer	158	0	339.4	0.0	142	0	292.1	0.0	**NA**	NA

Source: Table 11-89, CSR 013v1, p. 637

Reviewer's Comment: Because of the more comparable incidence rates of vaccine HPV related EGLs in subjects who were non-naïve for the relevant vaccine HPV type, the review team was more comfortable that there was no evidence of enhancement of vaccine HPV related EGLs in this seropositive and/or PCR positive subgroup. As with cervical disease related to vaccine HPV types, there will be additional data forthcoming from the close-out of Study 013 (and of Study 015) in the near future which should allow for a more definitive conclusion on vaccine effect in this subgroup.

Immunogenicity Results: Protocol 011

- The **primary immunogenicity objective** in Protocol 011 was to demonstrate that the concomitant administration of quadrivalent HPV vaccine and hepatitis B vaccine does not interfere with the immune response to either vaccine.
- The results of the immunogenicity analysis indicate that the quadrivalent HPV vaccine induced non-inferior immune responses, as measured by (1) the geometric mean titers (GMTs) of anti-HPV 6, 11, 16, and 18 at Week 4 following dose 3; and (2) the percentage of subjects who seroconverted for anti-HPV 6, 11, 16, and 18 by Week 4

Postdose 3, in subjects who received the quadrivalent HPV vaccine + hepatitis B vaccine and subjects who received quadrivalent HPV vaccine + hepatitis B placebo.

- The results also indicate that hepatitis B vaccine induced non-inferior immune responses, as measured by the percentage of subjects who achieved anti-HBs $\geq$ 10 mIU/mL by Week 4 following dose 3, in subjects who received the quadrivalent HPV vaccine + hepatitis B vaccine and subjects who received HPV placebo + hepatitis B vaccine.
- The results of the anti-HPV GMTs and seroconversion rates for each of the vaccine HPV types are shown in Table 113 below.

TABLE 113
Protocol 011: Summary of anti-HPV GMTs and Seroconversion Rates at Month 7 in the Subjects who Received Active HPV Vaccine With and Without Hepatitis B Vaccine (HPV PPI)

	HPV vaccine + Hep B **vaccine** N=466			HPV vaccine + Hep B **placebo** N=468		
		GMT (95% CI)	Number and Percentage who seroconverted (95% CI)		GMT (95% CI	Number and Percentage who seroconverted (95% CI)
HPV type	Number of subjects			Number of subjects		
HPV-6	274	**529.8** (483.3, 580.2)	274/274 **100%** (98.7, 100%)	306	**492.6** (452.9, 535.8)	306/306 **100%** (98.8, 100%)
HPV-11	274	**782.9** (706.9, 867.1)	274/274 **100%** (98.7, 100%)	306	**745.2** (675.2, 822.4)	305/306 **99.7%** (98.2, 100%)
HPV-16	262	**2236.3** (1939.1, 2579.1)	262/262 **100%** (98.6, 100%)	286	**2149.5** (1854.9, 2490.9)	286/286 **100%** (98.7, 100%)
HPV-18	305	**443.2** (395.1, 497.2)	303/305 **99.3%** (97.7, 99.9%)	332	**432.4** (385.9, 484.6)	329/332 **99.1**% (97.4, 99.8%)

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Tables 7-1 and 7-2, CSR 011, p. 174-5

- The reverse cumulative distribution curves are superimposable for all vaccine HPV type specific antibodies. (Source: Figure 7-1, CSR 011, P. 176, not shown here)
- The effect of dilution is discussed. In the assay validation analysis, higher dilutions tended to produce higher titers for all anti-HPV cLIAs. (See reviews by Dr. Lev Sirota and Dr. Rolf Tafts)
- **Comparison of HPV responses to HPV vaccine with or without Hepatitis B vaccine**
  - The anti-HPV GMT responses in the concomitant vaccines group were non-inferior to those in the quadrivalent HPV vaccine only group, because the sponsor's statistical criterion for similarity required that the lower bound of the confidence interval for the fold-difference in GMTs between the 2 groups [(HPV + hepatitis B vaccine]/ [HPV + placebo)] exclude a decrease of 2-fold or more for each HPV type. (See Table 114 below)

TABLE 114
Protocol 011: Statistical Analysis of Non-Inferiority Comparing Month 7 Anti-HPV cLIA GMTs Between Subjects who Received HPV Vaccine With and Without Hepatitis B Vaccine HPV PPI)

Assay	Comparison Group: HPV Vaccine + Hep B Vaccine Comparison Group A N=466		Comparison Group: HPV Vaccine + Hep B Placebo Comparison Group B N=468		Estimated Fold Difference Group A/Group B (95% CI)	p-value for non-inferiority
	N	**Estimated GMT (mmU/Ml)**	N	**Estimated GMT (mmU/Ml)**		
Anti-HPV 6	274	**615.7**	306	**475.0**	**1.30** (1.09, 1.54)	< 0.001
Anti-HPV 11	274	**906.0**	306	**706.6**	**1.28** (1.05, 1.56)	< 0.001
Anti-HPV 16	262	**2508.2**	286	**1923.7**	**1.30** (0.97, 1.75)	< 0.001
Anti-HPV 18	305	**483.2**	332	**431.5**	**1.12** (0.89, 1.41)	< 0.001

Source: Table 7-3, CSR 011, p. 179-80

- Also, the anti-HPV seroconversion responses in the concomitant vaccines group were non-inferior to those in the quadrivalent HPV vaccine only group. The sponsor's statistical criterion for similarity required that the lower bound of the confidence interval for the difference in proportions between the 2 groups [(HPV vaccine + hepatitis B vaccine) - (HPV vaccine + placebo)] exclude a decrease of 5 percentage points or more for each HPV type. This is shown in Table 115 below.

TABLE 115
Protocol 011: Statistical analysis of the Non-inferiority comparing Month 7 Seroconversion Rates in Subjects who Received the HPV Vaccine With or Without Hepatitis B Vaccine (HPV PPI population)

Assay	Comparison Group: HPV Vaccine + Hep B **Vaccine** Comparison Group A N=466		Comparison Group: HPV Vaccine + Hep B **Placebo** Comparison Group B N=468		Estimated Percentage Point Difference Group A-Group B (95% CI)	p-value for non-inferiority
	N	**Estimated Response (%)**	N	**Estimated Response (%)**		
Anti-HPV 6 ≥ 20 mMU/mL	274	**100.0%**	306	**100.0%**	**0.0** (-1.4, 1.3)	< 0.001
Anti-HPV 11 ≥ 16 mMU/mL	274	**100.0%**	306	**99.7%**	**0.3** (-1.1, 1.8)	< 0.001
Anti-HPV 16 ≥ 20 mMU/mL	262	**100.0%**	286	**100.0%**	**0.0** (-1.5, 1.3)	< 0.001
Anti-HPV 18 ≥ 24 mMU/mL	305	**99.3%**	332	**99.1%**	**0.2** (-1.6, 2.0)	< 0.001

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for anti-HPV 6, 11, 16, and 18 competitive Luminex immunoassay (cLIA) were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Table 7-4, CSR 011, p. 181-2

- **Anti-HBs RIA Responses**
  - **Hepatitis B GMTs:** A summary of the Hepatitis B GMTs by Vaccination Group are provided by group. The GMTs are well above 10 mIU/mL. The non-concomitant group had a higher GMT than the concomitant group. (See Table 116 below.) Results are similar for the all subjects with serology population. The pre-specified statistical criterion was based on seroconversion rates. (Source: Table 11-30, CSR 011, p. 341, not shown here)

TABLE 116
Protocol 011: Summary of Hepatitis B RIA GMTs by Vaccination Group (Hep B PPI)

	Gardasil + Hep B Vaccine N=466		Gardasil + Hep B Placebo N=468		HPV Placebo + Hep B Vaccine N=467		HPV Placebo + Hep B Placebo N=470	
Time Point	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
Day 1	341	<0.6 (<0.6, <0.6)	366	<0.6 (<0.6, <0.6)	363	<0.6 (<0.6, <0.6)	361	<0.6 (<0.6, <0.6)
Month 7	341	534.9 (433.8, 659.7)	366	<0.6 (<0.6, <0.6)	363	792.5 (654.0, 960.4)	361	<0.6 (<0.6, <0.6)

N=number of subjects randomized to respective vaccination group who eceived at least 1 injection.
n=number of subjects contributing to analysis; GMTs in mIU/mL; Source: Table 7-5, CSR 011, p.184

- **Hepatitis B Seroconversion Rates:** The sponsor's statistical criterion for NI requires that the lower bound of the confidence interval for the difference in proportions between the 2 groups [(hepatitis B vaccine [recombinant] + HPV) - (hepatitis B vaccine [recombinant] + placebo)] exclude a decrease of 10 percentage points or more). The seroconversion rates are 96.5% [95% CI: 93.9, 98.2%] for the concomitant group and 97.5% [95% CI: 95.3, 98.9%] for the non-concomitant group. This is shown in Table 117 below. The results are similar for the all subjects with serology population. (Source: Table 11-31, CSR 011, p. 342, not shown here)

TABLE 117
Protocol 011: Number (%) of Subjects with Hepatitis B RIA Titers ≥ 10 mIU/mL by Vaccination Group (Hep B PPI)

	Gardasil + Hep B Vaccine N=466		Gardasil + Hep B Placebo N=468		HPV Placebo + Hep B Vaccine N=467		HPV Placebo + Hep B Placebo N=470	
Time Point	n	Percent (95% CI)	n	Percent (95% CI)	n	Percent (95% CI)	n	Percent (95% CI)
Month 7	341	96.5% (93.9, 98.2%)	366	1.4 (0.4, 3.2%)	363	97.5% (95.3, 98.9%)	362	1.1% (0.3, 2.8%)

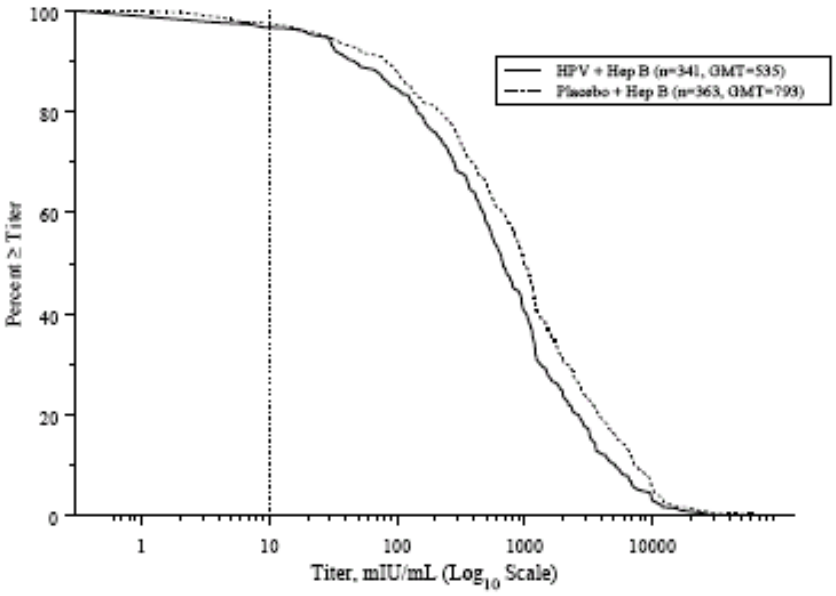
N=number of subjects randomized to respective vaccination group who eceived at least 1 injection.
n=number of subjects contributing to analysis
Percent is percentage of evaluable subjects with anti-HBS RIA ≥ 10 mIU/mL.
Source: Table 7-6, CSR 011, p. 185

- The RCDF curve for Hepatitis B in the concomitant group is slightly below the curve for the non-concomitant group. (See Figure 17 below.)

FIGURE 17
Protocol 011

Figure 7-2

Reverse Cumulative Distributions of Anti-HBs Titers at Month 7 –
Hepatitis B (Recombinant) Vaccination Groups
(Hepatitis B Per-Protocol Immunogenicity Population†)



† The per-protocol immunogenicity population for the Hepatitis B evaluation includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were anti-HBs seronegative at Day 1, and had a Month 7 anti-HBs serum sample collected within acceptable day ranges.

The vertical dotted line at 10 mIU/mL represents the seroprotection value for the anti-HBs.
n = Number of subjects contributing to the analysis; HBs = Hepatitis B surface antigen; HPV = Human papillomavirus; HPV + Hep B = Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine + Hepatitis B Vaccine (Recombinant) Group; Placebo + Hep B = Placebo (HPV Vaccine Matched) + Hepatitis B Vaccine (Recombinant) Group; mIU = Milli international units; GMT = Geometric mean titer.
Data Source: [4.3.7]

Source: Figure 7-2, CSR 011, p. 186,

- **Statistical Comparison of Hepatitis B Serum Responses:** The anti-HBs seroprotection responses in the concomitant vaccines group is non-inferior compared to the hepatitis B (recombinant) vaccine only group because the LB of the difference was < 10 percentage points (the pre-specified criterion for non-inferiority).

TABLE 118
Protocol 011: Statistical Comparison of Non-Inferiority Comparing Month 7 Anti-HBs Seroprotection Rates Between Subjects who Received Hepatitis B Vaccine With or Without HPV Vaccine (Hep B PPI)

Anti-HBs Response	Comparison Group: HPV Vaccine + Hep B **Vaccine** Comparison Group A N=466		Comparison Group: HPV Vaccine + Hep B **Placebo** Comparison Group B N=468		Estimated Percentage Point Difference Group A-Group B (95% CI)	p-value for non-inferiority
	N	**Estimated Response (%)**	N	**Estimated Response (%)**		
RIA≥10 mIU/mL	341	**96.5%**	363	**97.5%**	**-1.0** (-3.8, 1.7)	< 0.001

Source: Table 7-7, CSR 011, p. 188

Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine Versus Placebo (HPV Vaccine Matched) Summary of Anti-HPV Serum cLIA Responses

- No subjects in the PPI population who received HPV placebo were seropositive to **all 4 vaccine HPV types at Month 7.**
- Two subjects in the PPI population were seropositive to 2 vaccine HPV types at Month 7, and 16 who received the HPV placebo were seropositive to 1 vaccine type at Month 7.

Immunogenicity Results-Protocol 012

- The anti-HPV 16 GMTs and seroconversion rates in subjects who received the final manufactured product of the quadrivalent HPV vaccine were compared with the responses of subjects who received the Pilot Manufacturing Material of HPV 16 vaccine in Study 005. (See Table 119 below).

TABLE 119
Protocol 012: Summary of anti-HPV 16 GMTs and Seroconversion Rates at Month 7 in the subjects who Received Final Manufactured Product Quadrivalent HPV Vaccine Pilot Manufacturing Material Monovalent HPV 16 Vaccine (HPV PPI)

	FMP Quadrivalent HPV Vaccine N=1783			PMM Monovalent HPV 16 Vaccine		
		GMT (95% CI)	Number and Percentage who seroconverted (95% CI)		**GMT (95% CI**	Number and Percentage who seroconverted (95% CI)
HPV type	Number of subjects			Number of subjects		
HPV-16	1144	**2310.1 (2139.9, 2493.9)**	1142/1144 **99.8%** (99.4, 100%)	186	**1701.5 (1461.7, 1980.6)**	186/186 **100%** (98.0, 100%)

Seroconversion = change in serostatus from seronegative to seropositive. The cut-off for anti-HPV 16 competitive Luminex immunoassay (cLIA) was 20 mMU/mL.
Source: Tables 7-1, 7-2, CSR 012, p. 148-9

- There was one subject (AN 31354) who received FMP quadrivalent vaccine, and was seronegative to all 4 HPV types. There was one placebo recipient (AN 31993) seen at the same site on the same day who had high anti-HPV 6, 11, 16, and 18 antibody levels.
- There were 4 subjects who received the quadrivalent vaccine and did not have an immune response to one or more of the vaccine HPV types. (Source: Table 11-25, CSR 012, p. 289, not shown here)
- There were 31 subjects who received the placebo and had developed seropositivity to one of the vaccine HPV types. For the most part, the levels are generally similar to those who have had prior infection. (Source: Table 11-26, CSR 012, p. 290, not shown here)

Comparison of Anti-HPV 16 cLIA Responses

- Table 120 shows non-inferiority of the anti-HPV 16 **GMT responses** in the FMP quadrivalent HPV vaccine compared to the anti-HPV 16 GMT responses in the PMM HPV 16 vaccine by the predefined criterion that the LB of the CI for the fold-difference in proportions between the 2 groups (FMP quadrivalent/PMM HPV 16) exclude a decrease of 2-fold or more.

TABLE 120
Protocol 012: Statistical Analysis of Non-Inferiority Comparing Month 7 anti-HPV 16 cLIA GMTs between Subjects who Received Final Manufactured Product Quadrivalent Vaccine and Pilot Manufacturing Material Monovalent HPV 16 Vaccine (PPI Population)

	Comparison Group					
	FMP Quadrivalent HPV vaccine Comparison Group A N=1783		PMM Monovalent HPV 16 Vaccine Comparison Group B N=304		Estimated Fold Difference Group A/Group B (95% cI)	p-value for NI
Assay (cLIA)	N	**Estimated GMT (mMU/mL)**	N	**Estimated GMT (mMU/mL)**		
Anti-HPV 16	1144	**2045.1**	186	**1875.4**	**1.09** (0.86, 1.38)	<0.001

Source: Table 7-3, CSR 012, p. 154

- The **seroconversion rate** of the FMP quadrivalent HPV vaccine is also non-inferior to that of the PMM monovalent HPV 16 vaccine FMP quadrivalent HPV vaccine induces NI immune response, as measured by the percentage of subjects who seroconvert for HPV 16 by Week 4 following dose 3, to that induced by PMM HPV 16 vaccine. The pre-defined statistical criterion for NI required that the LB of the CI for the difference in proportions between the 2 groups (FMP quadrivalent – PMM HPV 16) exclude a decrease of 5% points or more. . (See Table 121 below.)

TABLE 121
Protocol 012: Statistical Analysis of Non-Inferiority Comparing Month 7 anti-HPV 16 cLIA Seroconversion Rates Between Subjects who Received Final Manufactured Product Quadrivalent HPV VLP Vaccine and Subjects who received Pilot Manufacturing Material Monovalent HPV 16 Vaccine (PPI)

	Comparison Group					
	FMP Quadrivalent HPV vaccine Comparison Group A N=1783		PMM Monovalent HPV 16 Vaccine Comparison Group B N=304		Estimated Percentage Point Difference (Group A – Group B) (95% CI)	p-value for NI
Assay (cLIA)	N	**SC**		**SC**		
Anti-HPV 16	1144	**99.8%**	186	**100%**	**-0.2** (-0.7, 1.9)	<0.001

Seroconversion = change in serostatus from seropositive to seronegative. Seropositive for anti-HPV 16 is a GMT $\geq$ 20 mMU/mL. Source: Table 7-4, CSR 012, p. 155

Exploratory Analyses of Persistence of Immune Response-Protocol 013
Initially naïve subjects:

- Almost all Gardasil recipients were seropositive at Month 7, and most remained seropositive at Month 24. However, the percentage of subjects who were seropositive to HPV 18 was lower than the other vaccine HPV types (74% at Month 24). (See Table 122 below.)

TABLE 122
Protocol 013: Summary of anti-HPV cLIA GMTs and Seropositvity Rates in Quadrivalent HPV Vaccinees in Protocol 013

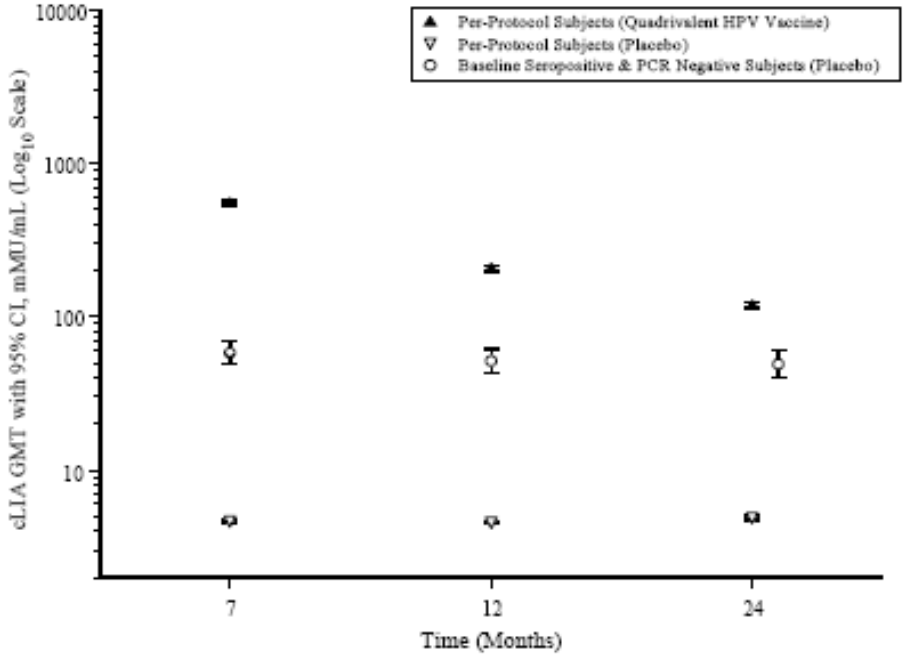
	Quadrivalent HPV Vaccine N=2717		
		GMT (mMU/mL) (95% CI)	Number and Percentage who seroconverted (95% CI)
HPV type	Number of subjects		
HPV-6			
Month 7	1773	551.3 (530.8, 572.5)	1770/1773 99.8% (99.5, 100%)
Month 12	1739	206.4 (197.9, 215.3)	1727/1739 99.3% (98.8, 99.6%)
Month 24	1655	118.1 (112.7, 123.8)	1581/1655 95.5% (94.4, 96.5%)
HPV-11			
Month 7	1773	786.7 (753.0, 822.0)	1769/1773 99.8% (99.4, 99.9%)
Month 12	1739	261.3 (250.0, 273.6)	1727/1739 99.3% (98.8, 99.6%)
Month 24	1655	152.2 (145.1, 159.6)	1622/1655 98.0% (97.2, 98.6%)
HPV-16			
Month 7	1694	2270.4 (2135.3, 2414.1)	1692/1694 99.9% (99.6, 100%)
Month 12	1662	909.9 (863.2, 959.0)	1655/1662 99.6% (99.1, 99.8%)
Month 24	1591	493.3 468.0, 520.0)	1583/1591 98.0% (97.2, 98.6%)
HPV-18			
Month 7	1903	466.1 (444.4, 489.0)	1894/1903 99.5% (99.1, 99.8%)
Month 12	1874	112.7 (106.3, 119.5)	1673/1874 89.3% (87.7, 90.6%)
Month 24	1781	55.5 (51.9, 59.3)	1310/1781 73.6% (71.4, 75.6%)

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for anti-HPV 6, 11, 16, and 18 cLIA are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: From Tables 7-32 and 7-33, CSR 013v1, p. 307-8

- Figures 18-21 are reproduced from CSR 013 p. 638-41, and demonstrate the longitudinal plots of anti-HPV 6, 11, 16, and 18 cLIA responses out to Month 24 in the PPE populations.

FIGURE 18
Protocol 013

Longitudinal Plot of Anti-HPV 6 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)

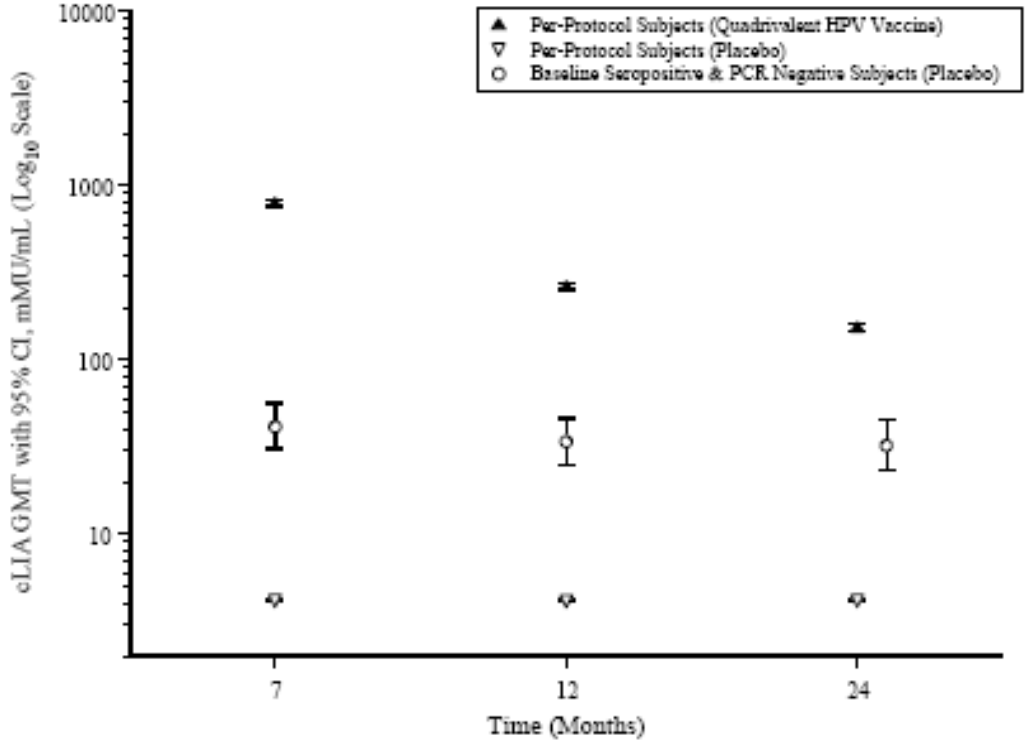


Population	Number of Subjects at Each Time Point (Months)		
	7	12	24
Quadrivalent HPV	1802	1774	1697
Placebo	1773	1739	1655
Baseline Seropositive & PCR Negative (Placebo)	138	131	125

Source: CSR 013v1, Figure 11-11, p. 638

FIGURE 19
Protocol 013

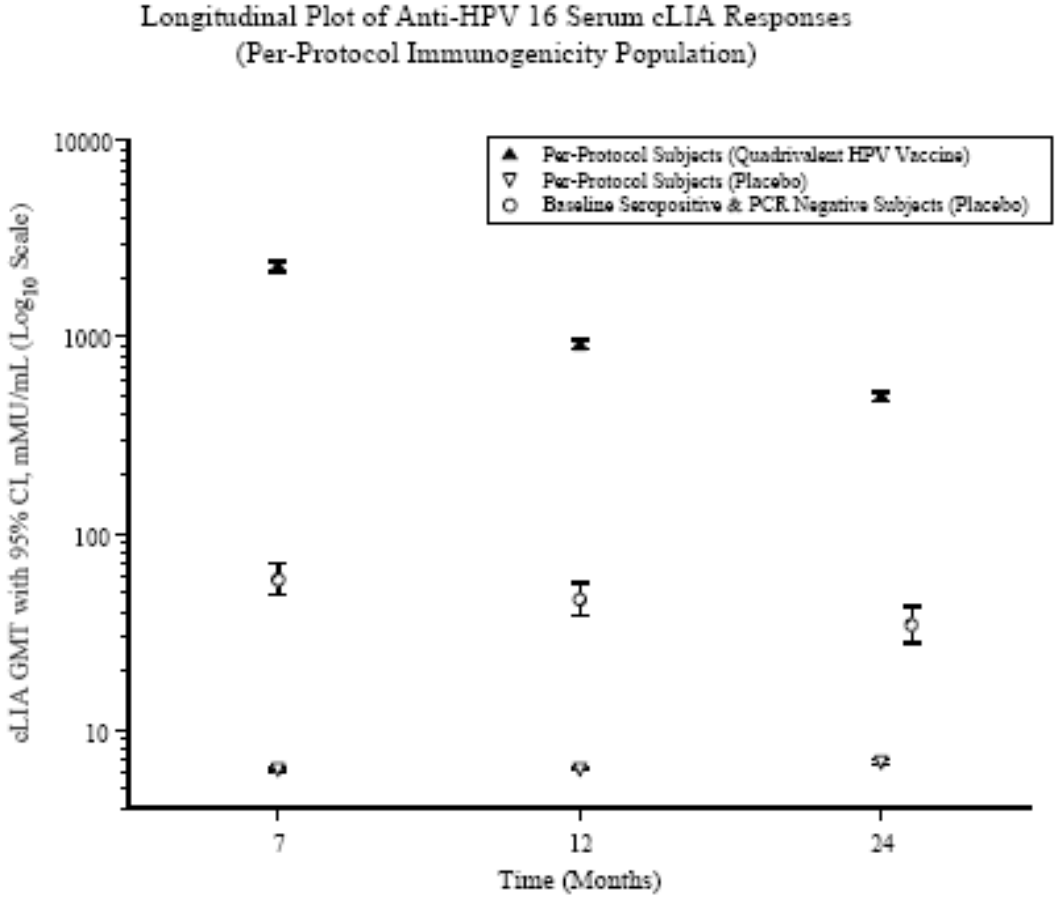
Longitudinal Plot of Anti-HPV 11 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Population	Number of Subjects at Each Time Point (Months)		
	7	12	24
Quadrivalent HPV	1802	1774	1697
Placebo	1773	1739	1655
Baseline Seropositive & PCR Negative (Placebo)	48	47	44

Source: CSR 013v1, Figure 11-12, p. 639

FIGURE 20
Protocol 013

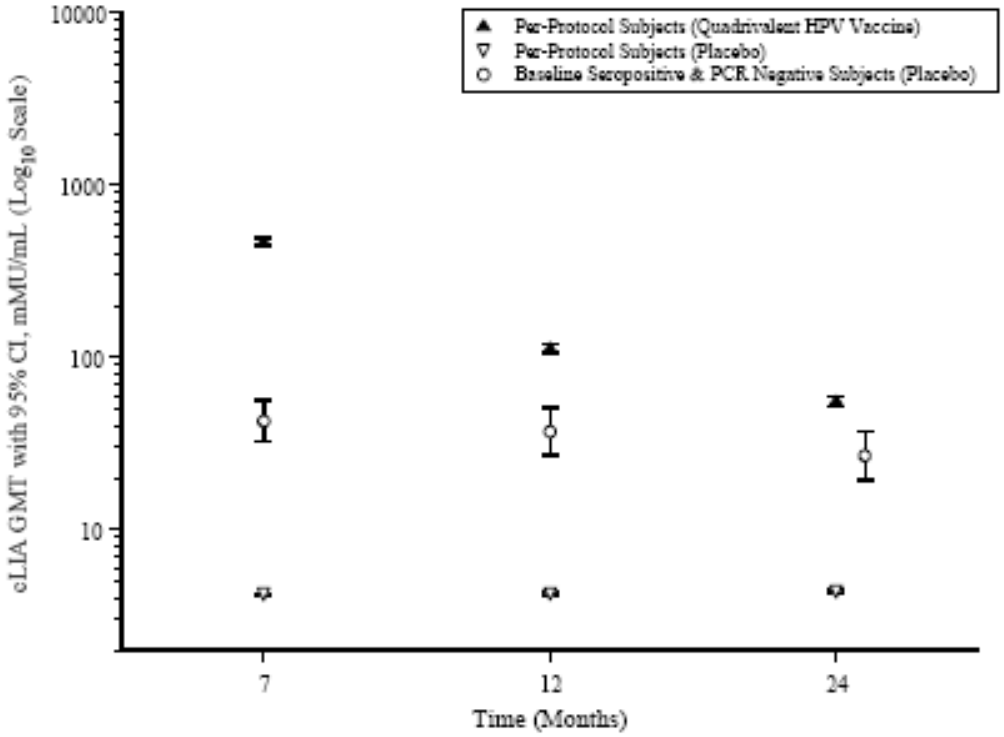


Population	Number of Subjects at Each Time Point (Months)		
	7	12	24
Quadrivalent HPV	1687	1663	1585
Placebo	1694	1662	1591
Baseline Seropositive & PCR Negative (Placebo)	185	173	169

Source: CSR 013v1, Figure 11-13, p. 640

FIGURE 21
Protocol 013

Longitudinal Plot of Anti-HPV 18 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)



Population	Number of Subjects at Each Time Point (Months)		
	7	12	24
Quadrivalent HPV	1931	1897	1812
Placebo	1903	1874	1781
Baseline Seropositive & PCR Negative (Placebo)	60	56	56

Source: CSR 013v1, Figure 11-14, p. 641

Impact of previous exposure to vaccine HPV types

- In general, subjects who were initially seropositive had a higher immune response than those who were initially seronegative through Month 24. This was true regardless of PCR status. Serostatus appeared to have a greater impact on the immune response than did PCR status.

Correlates of Protection

- No breakthrough cases of the co-primary efficacy endpoints were observed in the PPE population.
- In the MITT-2 population, 2 vaccinees developed a case of HPV 6, 11, 16, 18 related CIN or AIS, and 3 vaccinees developed a case of HPV 6, 11, 16, 18 related EGL.

Four of these subjects had a Month 7 anti-HPV response for the HPV type with which they became infected that was comparable to the GMT at Month 7 in the PPI population. One subject incorrectly received placebo and did not mount an immune response at Month 7. (These cases were previously discussed.)

Exploratory Analysis of Factors that May Potentially interfere with efficacy of the vaccine:

- **Sexual Activity:** The rate of new sexual partners was comparable between the vaccine and placebo groups.
- **Non-HPV Cervicovaginal Infection:** The incidences of Chlamydia and gonorrhea were comparable between the vaccine and placebo groups.

Safety Outcomes

Safety Population: All subjects who received at least one dose of vaccine or placebo were followed for safety.

Overall Adverse Events in Protocol 013

- The overall proportion of subjects who experienced at least one AE was slightly higher in the vaccine group.
- A larger proportion of vaccinees reported a local AE compared to placebo recipients.
- The proportion of subjects with a systemic AE was comparable between the vaccine and placebo groups.
- The proportions of subjects with SAEs were comparable between the vaccine and placebo groups.
- Few subjects discontinued due to an AE.
- One vaccine recipient and two placebo recipients died during the study.
- In Protocol 011, there was a higher incidence of AEs in all groups after dose 1 as compared to dose 2 and 3. This was also seen in Protocol 012, but to a lesser degree. Source: Tables 11-36, 11-37, 11-38, CSR 011, p. 347-52, and Tables 11-30, 11-31, and 11-32, CSR 012, p. 294-6, not shown here)
- There was no apparent difference in clinical AEs in those who were initially naïve or non-naïve for the vaccine HPV types. (Source: Tables 11-39, 11-40, CSR 011, p. 353-6, and Tables 11-33 and 11-34, CSR 012, p. 297-8, not shown here)

Summary of Intensities of AEs

- In both Protocols 011 and 012, in the 15 days after any vaccination, most subjects reported adverse experiences with the maximum intensity of mild or moderate. (Source: Tables 8-2 and 8-3, CSR 011, p. 198-9, and Tables 8-2 and 8-3, CSR 012, p. 162-3, not shown here)

TABLE 123
Protocol 013 Frozen File: Clinical Adverse Experience Summary
(Over Entire Study Period)

	Quadrivalent HPV Vaccine N=2713 n/%	HPV 16 Vaccine N=304 n/%	Placebo N=2724 n/%
Subjects with follow-up	2673	299	2672
N (%) with 1+ AE	2497 (93.4%)	278 (93.0%)	2405 (90.0%)
N (%) with IS AE	2353 (88.0%)	250 (83.6%)	2133 (79.8%)
N (%) with systemic AE	1744 (65.2%)	211 (70.6%)	1700 (63.6%)
N (%) with SAE	45 (1.7%)	4 (1.3%)	41 (1.5%)
Deaths	1 (0.04%)	0 (0.0%)	2 (0.1%)
D/C due to AE	3 (0.1%)	0 (0.0%)	8 (0.3%)
D/C due to SAE	1 (0.04%)	0 (0.0%)	3 (0.1%)

Source: Table 8-1, CSR 013v1, p. 324-5

- Because of differences in the end dates of studies 011, 012 (earlier), and 013 (later), there are **additional AEs included in Protocol 013** compared to Protocol 011 and Protocol 012. These were included in this review.
  - Subjects who died: 2 additional subjects (one vaccinee and one placebo recipient) are reported in the 013 CSR that were not reported in the 011 CSR (AN 25212 and AN 24657). One placebo recipient who died was already reported in the CSR for 011 (AN 25378).
  - SAEs: 12 subjects (5 vaccinees: AN 24412, 24597, 24815, 25212, and 31359 and 7 placebo recipients: AN 20386, 24399, 24657, 25402, 30830, 31094, and 32610) had an SAE that was included in CSR 013 but not 011 and 012. Of these, AN 24412, 24597, 24815, 31094, and 31359 were related to pregnancy.
  - Discontinuation due to an SAE: 2 subjects (1 vaccinee AN 25212 and 1 placebo recipient AN 24657).

Injection Site (IS) Adverse Events (Days 1-5 after vaccination)

- The most common IS AEs were pain, swelling and erythema.
- The proportion of specified IS AEs was slightly higher in the vaccine group compared to the placebo group.
- Most of the IS AEs were graded as mild to moderate in intensity.

Protocol 011 Injection Site (IS) AEs (Days 1-5)

- The sponsor presented the injection site adverse events in the 5 days after vaccination for Study 011 and Study 012 separately (substudies of Study 013). In Study 011, administration of Gardasil with or without Hepatitis B vaccine elicited isjection site pain in the highest proportion of vaccine recipients as compared to the other groups. (See Table 124 below).
- The proportion of subjects with an injection site AE in each treatment group in Study 012 is provided in Table 125.

TABLE 124
Protocol 011: Number (Percentage) of Subjects with Injection Site AEs (Incidence ≥ 1%) Days 1-5 after any Vaccination Visit

	HPV Vaccine + Hep B Vaccine (N=466)		**HPV Vaccine + Hep B Placebo** (N=468)		**HPV Placebo + Hep B Vaccine** (N=467)		**HPV Placebo + Hep B Placebo** (N=468)	
Subjects with f/u	458		463		458		464	
	HPV IS	Hep B IS	HPV IS	Hep B IS	HPV IS	Hep B IS	HPV IS	Hep B IS
N (%) with 1+ IS AE	395 (86.2%)	375 (81.9%)	385 (83.2%)	361 (78.0%)	359 (78.4%)	343 (74.9%)	351 (75.6%)	350 (75.4%)
IS Pain	387 (84.5%)	368 (80.3%)	381 (82.3%)	357 (77.1%)	354 (77.3%)	335 (73.1%)	343 (73.9%)	349 (75.2%)
IS Swelling	112 (24.5%)	93 (20.3%)	100 (21.6%)	76 (16.4%)	89 (19.4%)	75 (16.4%)	84 (18.1%)	82 (17.7%)
IS Erythema	78 (17.0%)	71 (15,5%)	86 (18.6%)	53 (11.4%)	70 (15.3%)	60 (13.1%)	50 (10.8%)	52 (11.2%)
IS Pruritus	25 (5.5%)	20 (4.4%)	23 (5.0%)	19 (4.1%)	21 (4.6%)	16 (3.5%)	15 (3.2%)	16 (3.4%)

Source: Table 8-4, CSR 011, p. 201-2

Protocol 012 IS AEs (Days 1-5)

TABLE 125
Protocol 012: Number (Percentage) of Subjects with Injection Site AEs (Incidence ≥ 1%) Days 1-5 after any Vaccination Visit

	FMP Quadrivalent Vaccine N=1779	PMM Monovalent Vaccine N=304	Placebo N=1789
Subjects with f/u	1752	299	1750
N (%) with 1+ IS AE	1539 (87.8%)	250 (83.6%)	1375 (78.6%)
IS Pain	1512 (86.3%)	242 (80.9%)	1330 (76.0%)
IS Swelling	482 (27.5%)	70 (23.4%)	256 (14.6%)
IS Erythema	495 (28.3%)	84 (28.1%)	338 (19.3%)
IS Pruritus	61 (3.5%)	12 (4.0%)	48 (2.7%)

Source: Table 8-4, CSR 012, p. 165

Injection site AEs post doses 1, 2, 3

- Injection-site adverse experiences reported within 5 days following each of vaccination Visit 1, Visit 2, and Visit 3 were generally similar to the results from the 2 tables above, except that in Protocol 012, differences in the proportions of subjects who reported injection site pain, erythema, or swelling between subjects in the quadrivalent group and subjects in the placebo group were more pronounced after

Dose 2 and Dose 3. (Source: Table 11-36, Table 11-37, and Table 11-38, p. 300-2; and Table 11-42, Table 11-43, and Table 11-44, p. 358-63, not shown here)

Systemic AEs (Days 1-15 after vaccination)

- In the 15 days after any vaccination, the most common systemic AE was headache, followed by pyrexia.
- In general, the proportions were comparable in the vaccine and placebo groups.
- Most were mild or moderate in intensity.
- In Table 126 below, systemic AEs are shown for each treatment group in Study 011. In Study 011, there was a somewhat higher proportion of subjects with pyrexia in subjects who received Gardasil as compared to subjects who received Gardasil placebo. Proportions of subjects with other systemic AEs are similar.

TABLE 126
Protocol 011: Number (%) of subjects with systemic AEs in Days 1-15 after any Vaccination Visit

Systemic AE	HPV Vaccine+ Hep B Vaccine N=466	HPV vaccine + Hep B Placebo N=468	HPV placebo + Hep B vaccine N=467	HPV + Hep B placebos N=468
Subjects with follow-up	458	463	458	464
	n/%	n/%	n/%	n/%
Headache	109 (23.8%)	126 (27.2%)	120 (26.2%)	121 (26.1%)
Pyrexia	95 (20.7%)	103 (22.2%)	73 (15.9%)	80 (17.2%)
Nausea	21 (4.6%)	30 (6.5%)	24 (5.2%)	25 (5.4%)
Nasopharyngitis	22 (4.8%)	16 (3.5%)	22 (4.8%)	17 (3.7%)
Influenza	17 (3.7%)	17 (3.7%)	19 (4.1%)	16 (3.4%)
Abdominal Pain	17 (3.7%)	19 (4.1%)	9 (2.0%)	9 (1.9%)
Pharynolaryngeal pain	16 (3.5%)	12 (2.6%)	20 (4.4%)	14 (3.0%)
Diarrhea	15 (3.3%)	13 (2.8%)	9 (2.0%)	15 (3.2%)
Back Pain	13 (2.8%)	10 (2.2%)	6 (1.3%)	10 (2.2%)
Dizziness	10 (2.2%)	11 (2.4%)	13 (2.8%)	14 (3.0%)
Dysmenorrhea	7 (1.5%)	10 (2.2%)	9 (2.0%)	10 (2.2%)
Cough	7 (1.5%)	6 (1.3%)	11(2.4%)	3 (0.6%)
Breast Pain	7 (1.5%)	6 (1.3%)	4 (0.9%)	1 (0.2%)

Source: From Table 8-10, CSR 011, p. 217-20

- In Study 012, the proportions of subjects with a systemic AE are similar in each treatment group.

TABLE 127
Protocol 012: Number (%) of subjects with systemic AEs in Days 1-15 after any Vaccination Visit

	FMP Quadrivalent HPV vaccine N=1779	PMM Monovalent HPV 16 vaccine N= 304	Placebo N=1789
Subjects with follow-up	1752	299	1750
Systemic AE	n/%	n/%	n/%
Headache	569 (32.5%)	104 (34.8%)	528 (30.2%)
Pyrexia	238 (13.6%)	33 (11.0%)	196 (11.2%)
Nausea	159 (9.1%)	23 (7.7%)	126 (7.2%)
Nasopharyngitis	148 (8.4%)	22 (7.4%)	127 (7.3%)
Dizziness	102 (5.8%)	18 (6.0%)	87 (5.0%)
Dysmenorrhea	89 (5.1%)	11 (3.7%)	81 (4.6%)
Influenza	90 (5.1%)	18 (6.0%)	78 (4.5%)
Pharynolaryngeal pain	81 (4.6%)	14 (4.7%)	82 (4.7%)
Diarrhea	76 (4.3%)	9 (3.0%)	70 (4.0%)
Abdominal Pain	52 (3.0%)	8 (2.7%)	63 (3.6%)
Back Pain	45 (2.6%)	10 (3.3%)	47 (2.7%)
Vomiting	46 (2.6%)	9 (3.0%)	46 (2.6%)
Cough	46 (2.6%)	6 (2.0%)	26 (1.5%)
Myalgia	38 (2.2%)	6 (2.0%)	42 (2.4%)

Source: From Table 8-9, CSR 012, p. 176-9

- Regarding the proportions of subjects with systemic AEs throughout the study period, there was a somewhat higher proportion of subjects with pyrexia in the Gardasil group (16.3%) as compared to the placebo group (13.0%). Further discussion regarding Temperature elevation is noted below.

TABLE 128
Protocol 013: Number (%) with Systemic AEs Days 1-9999 after any vaccination visit (Frozen File-8/11/05)

Systemic AE	Quadrivalent HPV Vaccine N=2713	Monovalent HPV Vaccine N=304	Placebo N=2724
Subjects with follow-up	2673	299	2672
Headache	805 (30.1%)	104 (34.8%)	769 (28.8%)
Pyrexia	436 (16.3%)	33 (11.0%)	348 (13.0%)
Nausea	210 (7.9%)	23 (7.7%)	175 (6.5%)
Nasopharyngitis	186 (7.0%)	22 (7.4%)	166 (6.2%)
Influenza	124 (4.6%)	18 (6.0%)	113 (4.2%)
Dizziness	123 (4.6%)	18 (6.0%)	115 (4.3%)
Pharynolaryngeal pain	109 (4.1%)	14 (4.7%)	116 (4.3%)
Dysmenorrhea	106 (4.0%)	11 (3.7%)	100 (3.7%)
Diarrhea	105 (3.9%)	9 (3.0%)	96 (3.6%)
Abdominal Pain Upper	82 (3.1%)	5 (1.7%)	87 (3.3%)
Fatigue	74 (2.8%)	12 (4.0%)	102 (3.8%)
Back Pain	68 (2.5%)	10 (3.3%)	63 (2.4%)
Vomiting	62 (2.3%)	9 (3.0%)	56 (2.1%)
Cough	59 (2.2%)	6 (2.0%)	40 (1.5%)
Pain in extremity	55 (2.1%)	7 (2.3%)	57 (2.1%)
Myalgia	50 (1.9%)	6 (2.0%)	55 (2.1%)
Malaise	47 (1.8%)	3 (1.0%)	40 (1.5%)
URI	36 (1.3%)	9 (3.0%)	42 (1.6%)
Asthenia	31 (1.2%)	7 (2.3%)	30 (1.1%)
Insomnia	35 (1.3%)	2 (0.7%)	23 (0.9%)
Somnolence	30 (1.1%)	0 (0.0%)	32 (1.2%)
Metrorhaggia	29 (1.1%)	3 (1.0%)	16 (0.6%)
Tonsillitis	26 (1.0%)	2 (0.7%)	29 (1.1%)
Nasal congestion	26(1.0%)	3 (1.0%)	15 (0.6%)
Arthralgia	27 (1.0%)	0 (0.0%)	25 (0.9%)

Source: From Appendix 4.4.8, CSR 013v1, p. 5036-69

Temperature Elevations Days 1-5 after Any Vaccination (See Table 129 below).

- The proportions of subjects with any temperature elevation were higher in the quadrivalent group as compared to placebo, and those groups had higher proportions than the monovalent HPV 16 vaccine group. The proportions with higher temperatures were similar in all groups.

TABLE 129
Protocol 013: Number (%) of subjects with elevated Ts Days 1-5 after any Vaccination Visit

	Quadrivalent HPV Vaccine	HPV 16 Vaccine	Placebo
	N=2713	N=304	N=2724
Subjects with f/u	2662	296	2666
Maximum T (Oral)	n/%	n/%	n/%
< 37.8 deg C	2268 (85.2%)	267 (90.2%)	2359 (88.5%)
>=37.8 deg C and < 38.9 deg C	354 (13.3%)	25 (8.4%)	274 (10.3%)
>=38.9 deg C and < 39.9 deg C	35 (1.3%)	3 (1.0%)	26 (1.0%)
>=39.9 deg C and < 40.9 deg C	5 (0.2%)	1 (0.3%)	4 (0.2%)
>=40.9 deg C	0 (0.0%)	0 (0.0%)	3 (0.1%)

Source: Appendix 4.4.10, CSR 013v1, p. 5070

Significant/Potentially Significant Events

Deaths: There were 3 deaths reported in Protocol 013.

- **AN 25212:** 19 year old bf received 3 doses of **HPV vaccine and Hepatitis B vaccine** on 2/26/03, 4/30/03, and -------. On ------, at **Day 342 postdose 3, the subject suffered severe head trauma in an MVA** and died.
- **AN 24657:** 23 year old wf with a history of menstrual irregularity, obesity, insulin resistance, diarrhea and UTI received **HPV placebo and Hepatitis B placebo** on 12/18/02, 2/17/03, and -------. The subject started in OCPs on 6/10/03. On -------, **202 days postdose 3 placebo**, the subject experienced malaise. She went to the hospital and was treated and released. On Day 204, she returned to the hospital and died. Her diagnoses included a DVT, PE, renal insufficiency, and shock lung, all severe.
- **AN 25378**: 19 year old wf received **HPV placebo and Hepatitis B vaccine** on 3/11/03 and -------. On ------- **(1 day postdose 2),** she died as a result of trauma sustained in an MVA. This was considered to be probably not related to vaccination.

Reviewer's Comment: Two of the deaths occurred after receipt of HPV placebo and one after HPV vaccine. The HPV vaccine recipient died almost a year after the last dose in an MVA. One subject who received the HPV placebo and Hepatitis B vaccine died 1 day after dose 2 in an MVA.

Serious Adverse Events

- SAEs are shown in Table 130 below.

TABLE 130
Protocol 013: SAEs in Vaccinees

AN	Event	Days Post dose	Duration	Outcome	Action
* see below	OD	1 day postdose 1 (except for 2 with 1 day postdose 2 and 1 day postdose 3)	1 day	Recovered	Subjects received 3 doses
		GI			
31683	Cholecystitis (severe) Cholethiasis (severe)	5 days postdose 1 5 days postdose 1	13 days 13 days	Recovered	Received Doses 2 and 3
33757	Gastroenteritis (moderate)	8 days postdose 1 (HPV+Hep B)	5 days	Recovered	Received Doses 2 and 3
24033	Appendicitis (severe)	1 day postdose 2	2 days	Recovered	Received Dose 3
32653 (monovalent)	Enterocolitis infection (severe)	7 days postdose 3	3 days	Recovered	NA
INJURY					
25212	Head injury	373 days postdose 3 (HPV + Hep B)	1 days	Fatal	Discontinued
30663	Polytrauma (severe)	10 day postdose 1	2.27 months	Recovered	Received Dose 2, lost to follow-up
		NEURO			
31157	Headache, severe	11 days postdose 2	4 days	Recovered	Received Dose 3
		RESP.			
30749	Asthma (moderate) (worsening)	1 day postdose 1	28 days	Recovered	Received Doses 2 and 3
32751	Hyperventilation (severe) (history of same)	15 days postdose 1	2 days	Recovered	Received Doses 2 and 3
32448	Bronchospasm (severe) (no history) – possibly related per investigator	1 day postdose 3	2 days	Recovered	Had facial edema postdose 2, possible allergy
		INFECTION			
31079	Tonsillitis (severe)	7 days postdose 1	5 days	Recovered	Received 3 doses
30156	Condyloma acuminata (moderate)	15 days postdose 2	3 days	Recovered	Received Dose 3
31666 (Monovalent)	Breast abscess in pregnancy (severe)	184 days postdose 2	11 days	Recovered	Received Dose 3

TABLE 130 [(Cont.)] Protocol 013: SAEs in Vaccinees

AN	Event	Days Post dose	Duration	Outcome	Action
OB/GYN and GU					
31101	PID (severe) UTI (severe)	6 days postdose 2	4 days	Recovered	Received Dose 3
30252	PID (moderate) (removed IUD)	1 day postdose 2	9 days	Recovered	Received Dose 3
32536	UTI (moderate) (Subsequent delivery)	229 days postdose 2	4 days	Recovered	Received Dose 3
24090	Pyelonephritis (severe)	7 days postdose 3 (HPV+Hep B)	3 days	Recovered	NA
24815	Pyelonephritis (severe) Prolonged labor (severe)	43 days postdose 3 272 days postdose 3	`4 days 1 day	Recovered Recovered	NA
24934**	Transverse presentation	403 days postdose 2 (HPV+Hep B)	1 day	Recovered	No write-up
24658	Premature Labor (moderate) Preeclampsia (mild) Anemia (moderate)	215 days postdose 1 AND 251 days postdose 1	2 days each	Recovered	Received Doses 2 and 3
20126	CPD	262 days postdose 1 (HPV+ HepB)	1 day	`Recovered	Received Doses 2 and 3
24412	PROM possibly related to LEEP (severe)	550 days postdose 3 (HPV+HepB)	4 days	Recovered	Received Doses 2 and 3
30629	Breech presentation (severe)	261 days postdose 2	3 days	Recovered	Received Dose 3
30580	Fetal malposition (moderate) Operative hemorrhage (severe)	272 days postdose 1	1 day	Recovered	Received Doses 2 and 3
30721	PROM (moderate)	255 days postdose 1	7 hours	Recovered	Received Doses 2 and 3
31359	Oligohydramnios (moderate)	617 days postdose 2	4 days	Recovered	Further doing not stated
33168	CPD (mild) Prolonged labor (moderate)	348 days postdose 2	13 hours	Recovered	Received Dose 3
20512	Hypotension during delivery (moderate)	295 days postdose 1 (HPV+HepB)	2 hours	Recovered	Received Doses 2 and 3
20388	Cervical dystocia in pregnancy (severe)	426 days postdose 2 (HPV+Hep B)	1 day	Recovered	Withdrew consent
25205	Cervix dystocia in pregnancy (severe)	254 days postdose 1	1 day	Recovered	Received Doses 2 and 3
24511	Cervix dystocia in pregnancy	255 days postdose 2	4 days	Receovered	Received Dose 3
24597	Cervix dystocia in pregnancy (severe)	251 days postdose 3	4 days	Recovered	NA

*****Includes AN 30939, 31950 [monovalent 16], 24046, 24739, 20162, 30938, 30940, 30945, 30947, 30948, 30949, 31939, 31941, 31942, 31946, 31948, 31949 [quadrivalent] who received inadvertently 0.75 mL HPV vaccine or 1 mL Hepatitis B vaccine if < 20 years of age.
** Cannot locate case report

- There were SAEs reported in 91 subjects from the time of screening through the efficacy analysis. There were 45 quadrivalent HPV vaccine recipients, 42 placebo

recipients, and 4 monovalent HPV 16 recipients (substudy 012). In addition, there was one subject with an SAE who was randomized but did not receive vaccine.

- 60/91 subjects had **non pregnancy** related SAEs (29 quadrivalent vaccine, 28 placebo, 3 monovalent vaccine). These included 2 subjects in Study 011 who developed SAEs Day 8 after the Month 18 vaccination with Dose 1 Hepatitis B vaccine (initially received Hepatitis B placebo): AN 20386 had an accidental ingestion; and AN 25402 developed Bell's palsy. These also included 1 subject (AN 30830) who developed an SAE related to a study procedure and 1 subject (AN 32448) who developed severe bronchospasm on the day of receipt of vaccine of 2 days duration. This was considered possibly vaccine related.
- 36 additional subjects (15 quadrivalent vaccine, 2 monovalent vaccine, 19 placebo) received 0.75 mL HPV study material instead of 0.5 mL, and these were considered overdoses (7 subjects received 2 such doses). One of these subjects received 1.0 mL Hepatitis B vaccine even though this subject was < 20 years of age. This event was considered an overdose, since subjects < 20 years of age were to receive 0.5 mL Hepatitis B vaccine IM.
- 31/91 had **pregnancy related** SAEs (16 quadrivalent vaccine, 14 placebo, 1 monovalent). (It is noted that 7 were reported after closure of databases for substudies substudies 011 and 012.) 1 was randomized but developed a moderate genital herpes infection prior to vaccination.
- The **placebo recipients** had SAEs that were similar to those of vaccinees. These included: 24 [in 19 subjects] inadvertent overdoses; 1 with an abdominal injury; 1 death after an MVA at 1 day postdose 2 of HPV placebo and Hepatitis B vaccine (AN 24657); 1 with facial palsy 373 days postdose 3 HPV placebo but 9 days postdose 1 Hepatitis B (24502); 1 with a convulsion and headache 3 days postdose 2 placebo; 1 with accidental poisoning from garden material at day 8 postdose 1 hepatitis B; 1 with endometritis deciduas with pregnancy; 1 with postprocedural hemorrhage; one with dizziness with pregnancy; one with an intervertebral disc problem; 1 with syncope; 1 with infectious colitis; 3 with preeclampsia; 1 with premature labor; 1 with fetal distress; 1 with a breech presentation; 1 with CPD; 2 with failed induction of labor; 1 subject with a threatened abortion twice in the same pregnancy (the child had varicella and cord around the neck); 1 with oligohydramnios; 1 with toxemia; and 1 death due to a PE with ARDS and DVT.
- The percentage of subjects who had SAEs Days 1-15 following any vaccination is shown in Table 131 below, and the proportions are similar in each group.

TABLE 131
Protocol 013: Comparison of Vaccination Groups with Respect to Number (%) of Subjects who Reported SAEs Days 1-15 After Any Vaccination Visit

	Quadrivalent HPV Vaccine N=2713	Placebo N=2724	Risk Difference (Vaccine – Placebo) 95% CI
Subjects with follow-up	2673	2672	
Subjects with SAE Days 1-15 after any vaccination visit	27 (1.0%)	24 (0.9%)	0.1 (-0.4, 0.7)

From Table 8-5, CSR 013v1, p. 365

AEs that led to discontinuation

- 12 subjects (4 vaccinees and 8 placebo recipients) experienced an AE that led to discontinuation. In addition, 1 subject discontinued because of an AE bit this occurred after screening but before receiving any vaccination. The 4 vaccine recipients who discontinued due to an AE included:
  - **AN 25212:** The 19 year old wf discontinued due to fatal head injury 372 days postdose 3 Gardasil. (This subject also had flu with moderate headache and fever and moderate IS pain postdose 1, and mild IS pain postdose 2 and 3.)
  - **AN 32107**: 22 year old mf discontinued due to facial swelling after dose 1 vaccine. IS pain also was noted postdose 1.
  - **AN 32513**: 20 year old wf discontinued due to nausea, diarrhea, and vomiting postdose 1 vaccine, moderate in intensity.
  - **AN 20049**: 23 year old wf had diffuse IS pain after dose 2 vaccine. This lasted 3 months, was mild, and caused no further vaccine to be given.
- Placebo recipients discontinued from the study due to injection site pain; fatal DVT, PE, ARDS, and renal failure; fatal MVA; herpes zoster; allergic edema; eczema; syncope; and injection site reaction.

Pregnancy Outcomes

- All pregnancies during the study period were reported and followed for outcome.
- Overall, 707 women in Protocol 013 reported 776 pregnancies during the entire study period.
- The proportion of live births and fetal losses were comparable between the two groups.
- Among the live births, the proportions of C-sections and vaginal deliveries were comparable between the two groups.
- The outcomes of the live births were comparable between the two groups.
- There were 12 infants in each group with abnormalities other than congenital anomalies.
- In the fetal losses, there were 2 infants in the vaccine group with a congenital anomaly and 3 in the placebo group.

TABLE 132
Protocol 013: Pregnancy Outcome Summary

	HPV Quadrivalent Vaccine N=2731	HPV 16 Vaccine N=304	Placebo N=2724
Subjects with Pregnancies	357 (13.2%)	29 (9.5%)	321 (11.8%)
Number of pregnancies	388	37	351
Number of pregnancies with unknown outcome	77	7	66
Number of fetuses/infants with known outcome	315	31	289
Live Births	187 (59.4%)	16 (51.6%)	171 (59.2%)
Infant Outcome			
Normal	170 (90.9%)	15 (93.8%)	152 (88.9%)
Abnormal Congenital Anomaly Other Medical Condition	15 (8.0%) 5 (2.7%)* 12 (6.4%)	1 (6.3%) 0 (0.0%) 1 (6.3%)	19 (11.1%) 7 (4.1%)* 12 (7.0%)
Unknown	2 (1.1%)	0 (0.0%)	0 (0.0%)
Fetal Loss	128 (40.6%)**	15 (48.4%)	118 (40.8%)**
Spontaneous Abortion	93 (72.7%)***	9 (60.0%)	76 (64.4%)***
Late Fetal Death	3 (2.3%)	0 (0.0%)	2 (1.7%)
Elective Abortion	31 (24.2%)	6 (40.0%)	40 (33.9%)
Fetal Outcome (of Fetal Losses)			
Normal	8 (6.3%)	1 (6.7%)	2 (1.7%)
Abnormal Congenital Anomaly Other medical condition Unknown	3 (2.3%) 0 (0.0%) 2 (1.6%) 116 (90.6%)	0 (0.0%) 0 (0.0%) 0 (0.0%) 14 (93.3%)	3 (2.5%) 0 (0.0%) 3 (2.5%) 113 (95.8%)

*Percentage based on number of live births.
**Percentage based on number of infants with known outcomes.
***Percentage based on number of fetal losses. See text below.
From Table 8-6, CSR 013v1, p. 367-8

- It was noted that the rate of spontaneous abortions was higher in vaccine recipients [93/315 known outcomes = 29.5%] as compared to placebo recipients [76/289 known outcomes = 26.3%]. There was one extra subject who received placebo HPV and Hep B at dose 1, then was given HPV vaccine and Hep B placebo at dose 2, and had a spontaneous abortion. This subject is not included in Table 132 above. [This subject had a spontaneous abortion after receiving the HPV vaccine and should be added to the above tallies. This would increase the percentage of spontaneous abortions to 94/316 = 29.7%] in HPV vaccinees] See Overall Safety Summary for proportions in all studied combined.)

Congenital Anomalies

- There was a higher proportion of congenital anomalies noted in the placebo recipients [7/171 = 4.1%] compared to vaccine recipients [5/187 = 2.7%]
  - There were 5 congenital anomalies in the vaccine group (including hip dysplasia, tricuspid valve disease, congenital hydronephrosis, 1 infant with lower limb

malformations and low set ears; and 1 infant with pyloric stenosis and congenital ankyloglossia.) 2/5 occurred within 30 days of vaccination.

- There were 7 congenital anomalies in the placebo group (including 1 with adactyly, congenital hydronephrosis, bilateral inguinal hernia, exomphalos, and cleft lip and palate; 1 with congenital hip deformity, exomphalos, and ASD; and 1 with ASD and VSD.) 0/5 occurred within 30 days of vaccination.
- In the monovalent HPV 16 group, there were no congenital anomalies.

Reviewer's Comment: An overall summary of timing of conception and the occurrence of congenital anomalies is discussed in the overall discussion of safety of the vaccine.

SAEs during pregnancy

- These are included in Table 131 above of SAEs in vaccinees. The medical events appear to be comparable between the vaccine and placebo groups. (Source: Table 8-8, 013v1, p. 376-9, not shown here)

Lactation

- There were no SAEs reported in vaccinated subjects during lactation.

Infant SAEs:

- Overall, 22 subjects in the quadrivalent vaccine group, 26 in the placebo group, and 2 in the monovalent vaccine group had an infant with an SAE.
- There were 4 infant deaths overall: 1 in the quadrivalent vaccine group; 2 in the placebo group; and 1 in the monovalent group. Table 133 below is a reviewer constructed table which presents these SAEs.

TABLE 133
Protocol 013: SAEs in Infants Born to Vaccine Recipients

AN of mother	Event in infant	Days postdose event occurred	Outcome
20420	Severe bronchial obstruction and diarrhea	155 days postdose 3 (Lactation)	Recovered
20497	Premature birth, small for dates	658 days postdose 3	Recovered
24012	Bronchitis	22 days postdose 3 (lactation)	Recovered
24016	Jaundice	772 days postdose 3 and 426 days postdose 3 of active hepatitis B vaccine	Recovered
24085	Nephrolithiasis	703 days postdose 3	Recovered
24090	Omphalitis	497days postdose 3	Recovered
24636	Viral meningitis	477 days postdose 3	Recovered
24658	Premature delivery of twins: Twin A had hip dysplasia	251 days postdose 1	Recovered with therapy
24815	Neonatal anoxia Neonatal sepsis	266 days postdose 3	Recovered
24836	Premature delivery at 28 weeks, uterine hemorrhage (mother with history of late fetal losses in past pregnancies). This child had low set ears and lower limb malformation and respiratory distress syndrome.	473 days postdose 3	Child died
25142	Premature birth of twins: Twin A had atelectasis, cardiorespiratory arrest. Twin B had conjunctivitis, jaundice and laryngitis; later this twin had bronchiolitis and dehydration (see overall summary for outcome after study report submission).	521 days postdose 3	Recovered
25205	Severe pneumonia Gastroenteritis	167 days postdose 3 (lactation) app. 2 months after above	Recovered Recovered
25271	Oligohydramnios, transitory tachypnea	245 days postdose 1	Recovered
25428	Premature birth, Electrolyte imbalance, tricuspid incompetence	571 days postdose 3	Recovered
30580	Pyloric stenosis, ankyloglossia congenital	272 days postdose 1	Recovered with surgery Ongoing
31291	Mother with subcorial hematoma Neonatal aspiration of meconium	147 days postdose 1 304 days postdose 1	Recovered Recovered
31307	Left thigh cellulitis	84 days postdose 2 (Lactation)	Recovered
31702	Neonatal respiratory distress syndrome and jaundice	743 days postdose 3	Recovered
32296	Premature birth Possible neonatal infection	246 days postdose 2	Recovered
32536	Bronchiolitis Bronchiolitis	150 days postdose 3 (Lactation) 386 days postdose 3	Recovered Recovered
33319	Congenital hydronephrosis	291 days postdose 2	Ongoing, mother withdrew
33654	Bronchioliotis	112 days postdose 2 (lactation)	Recovered

From narratives CSR 013v1, p. 683-90 and Tables 8-9 and 8-10, p. 383-95

- The SAEs that occurred in infants whose mothers received HPV placebo include the following: Small for dates baby; bronchopneumonia (lactation); premature birth; asthmatic bronchitis; twins with neonatal respiratory distress; child born with exomphalos; viral infection (lactation); bilateral inguinal hernia; bronchiolitis,

pneumonia, anemia; pneumonia (lactation); pneumonia after preeclampsia; UTI (Lactation); prematurity with death at birth; pneumonia; cleft lip and palate; prematurity with neonatal respiratory distress; adactyly; hip dysplasia and ASD; neonatal jaundice; neonatal respiratory distress; hydronephrosis; neonatal jaundice (mom with threatened abortion x 2); prematurity, dyspnea, jaundice; twins with respiratory distress; ASD and VSD; prematurity; pneumonia and pulmonary hypertension; and gastrointestinal necrosis.

- **SAEs during lactation in babies**: There were 3 in each group.

New Medical Conditions Day 1 through Month 7

- The most common new medical conditions reported in subjects from Day 1 through Month 7 were headache and nasopharyngitis.
- Other more common new medical conditions include influenza, vaginal candidiasis, and bacterial vaginosis.
- The proportions of subjects reporting a new medical condition were generally comparable among the quadrivalent HPV vaccine recipients, the monovalent HPV vaccine recipients, and the placebo recipients. (Source: Table 8-11, CSR 013v1, p. 398-403, not shown here).
- There were 2 cases of RA in the placebo group and 1 in the vaccine group. There were 3 cases of juvenile arthritis in the vaccine group (although in a follow-up report, 2 of 3 appear to have had symptoms **prior to vaccination**), and 0 in the placebo group. Overall, the numbers of subjects with musculoskeletal complaints were comparable between the quadrivalent HPV vaccine and the placebo groups. (These were noted on the list of new medical conditions > 0%, Appendix 4.4.12, CSR 013v1, p. 5139-5203, not shown here).

Reviewer's Comment: CBER requested an analysis of autoimmune conditions over the entire safety database, and these events are discussed in the assessment of safety overall.

- The sponsor notes that there were subjects with additional new medical conditions that were not reported in the CSRs for 011 and 012. These included 2 subjects with amenorrhea; 1 with pyrexia; 1 with psoriasis (AN33600), and 1 with bacterial food poisoning, chemical poisoning, hemorrhoids and a suicide attempt. These additional data did not impact on the conclusions for Protocols 011 and 012. [It is noted that the incidence of new cases of psoriasis in the quadrivalent vaccine group was 0.5%, and 0.3% in the placebo group.]

New Medical Conditions in post-month 7 period

- The most common new medical condition in the post-Month 7 period were bacterial vaginitis and vaginal candidiasis.
- The proportions of subjects with new medical conditions in each group were generally comparable. (Source: Table 8-12, CSR 013v1, p. 405-10, and Table 11-93, p. 701-63, not shown here).

Comments-Conclusion Regarding Data for Protocol 013 (Reviewer's Opinion)
Efficacy:

- Study 013 demonstrated a high level of efficacy for the quadrivalent HPV vaccine in the prevention of **vaccine type HPV related CIN** (VE = 100%; 95% CI: 87.4, 100%) and in the prevention of **vaccine type HPV related EGL** (VE = 100%; 95% CI: 88.4, 100%) in the PPE population.
- HPV 6, 11, 16, 18 related CIN Endpoint (Co-Primary Endpoint):
  - VE against each vaccine type HPV related CIN was 100% (95% CI: 87.4, 100%) in the PPE.
    - HPV 6 CIN 95% CI: 30.3, 100%
    - HPV 11 CIN 95% CI: <0.0, 100%
    - HPV 16 CIN 95% CI: 82.1, 100%
    - HPV 18 CIN 95% CI: 41.2, 100%
  - VE against vaccine related specific CIN diagnoses was 100% in the PPE:
    - CIN 1 95% CI: 84.1, 100%
    - CIN 2 or worse 95% CI: 79.7, 100%
    - CIN 2 95% CI: 69.7, 100%
    - CIN 3/AIS 95% CI: 55.2, 100%
  - **MITT-1 population** (like PPE with protocol violators): The VE was 100% (95% CI: 90.1, 100%), and was seen for each vaccine HPV type and the different vaccine HPV type related CIN diagnoses.
  - **MITT-2 population** (vaccine HPV naïve, cases occurring more than 30 days after dose 1): One additional vaccinee developed HPV 6 related CIN 1 day Day 6 postdose 2. In this population, the VE was 96.5% (95% CI: 86.7, 99.6%).
  - **MITT-3 population** (included regardless of baseline HPV PCR and serology status): There were many more cases in the vaccine and placebo groups, and all cases which occurred in Gardasil recipients were in those positive for the relevant HPV type at baseline. The overall VE was 42.9% (95% CI: 21.9, 58.6%). Even though the VE ranged from 32% (95% CI: 2.3, 52.8%) for HPV 16 CIN and 100% (95% CI: 49.5, 100%) for HPV 11 CIN, it is noted that the VE for CIN 2 or worse was 22.8% (95% CI: <0.0, 48.2%).
- HPV 16/18 CIN (Secondary VE endpoint for this study):
  - In the PPE, the VE in preventing HPV 16/18 CIN was 100% (95% CI: 85.8, 100%).
  - VE was 100% against HPV 16 related CIN (95% CI: 82.1, 100%) and HPV 18 related CIN (95% CI: 41.2, 100%) in the PPE.
  - VE was 100% against HPV 16/18 related CIN 1 (95% CI: 75.5, 100%), CIN 2 or worse (95% CI: 78.5, 100%), CIN 2 (95% CI: 76,100%), CIN 3 (95% CI: 41.1, 100%) and AIS (95% CI: <0.0, 100%) in the PPE.
- HPV 6, 11, 16, 18 related EGL Endpoint (Co-Primary endpoint):
  - VE against each vaccine HPV type related EGL was 100% (95% CI: 88.4, 100%) in the PPE.
    - HPV 6 CIN 95% CI: 82.5, 100%
    - HPV 11 CIN 95% CI: 55.1, 100%
    - HPV 16 CIN 95% CI: 56.3, 100%
    - HPV 18 CIN 95% CI: <0.0, 100%

- VE against vaccine related specific EGL diagnoses was 100% in the PPE:
  - Condyloma accumniata, VIN 1, VaIN1 (95% CI: 88.5, 100%)
  - VIN 2/3 or VaIN 2/3 (95% CI: 30.2, 100%)
- Regional VE against vaccine HPV related EGL in PPE: 100% in all 4 geographic areas.
- **MITT-1 population** (like PPE with protocol violators): The VE was 100% and additional cases occurred in the placebo group.
- **MITT-2 population** (vaccine HPV naïve, cases occurring more than 30 days after dose 1): There were 3 cases in the vaccine recipients. 1 subject developed HPV 6 infection at Month 3 and then developed HPV 6 related condyloma accuminata at Month 12. 1 subject developed HPV 6 infection at Month 3, and went onto develop HPV 6 related VIN 1 at 21 days after Month 7. 1 subject developed HPV 11 infection at Month 7. At 3 months after Month 18, the subject developed HPV 11 related condyloma accuminata and VaIN 1. VE remained >90% to 100% for all vaccine related HPV type EGL and specific EGL diagnoses. The LB of any CI was $\geq$ 30.1%.
- **MITT-3 population** (analyzed regardless of baseline HPV PCR and serology status): There were many more cases in the vaccine and placebo groups, and all cases occurred in those positive for the relevant HPV type at baseline. The overall VE was 67.8% (95% CI: 49.3, 100%). The VE ranged from 63% for HPV 6 EGL to 87.5% for HPV 11 EGL and HPV 18 EGL. The VE against vaccine HPV related VIN 1 or VaIN 1 was 69.7% (95% CI: 50.6, 82.1%), and VE against VIN 2/3 or VaIN 2/3 was 63.7% (95% CI: < 0.0, 91.6%).

- **HPV 6, 11, 16, 18 related disease**
  - In the PPE, the VE against all vaccine HPV related genital disease was also 100% in the PPE (95% CI: 94.6%, 100%). The VE against each vaccine HPV type related disease was also 100% with the LB of the 95% CI at least 55.1%.
  - In the MITT-3 population, the VE against all vaccine HPV related genital disease was 50.4% (95% CI: 35.4, 62.1%).
  - In vaccinees who received the monovalent HPV 16 vaccine, there were no subjects in the PPE, MITT-1, MITT-2, MITT-4 populations who developed HPV 16 related CIN or EGL. In the MITT-3 population, 6 vaccinees developed HPV 16 related CIN and 2 vaccinees developed HPV 16 related EGL, but these subjects were non-naïve to HPV 16 at baseline.
- **Other Efficacy Analyses**
  - Analysis of VE against all HPV related CIN (restricted MITT-2): Overall, the VE was 24.9% (95% CI: 2.2, 42.5%).
  - Analysis of VE against all HPV related CIN (MITT-3): Overall, the VE was 16.6% (95% CI: 1.8, 29.1%). However, there were more cases of CIN 3/AIS in the vaccine group as compared to placebo. CBER had requested analyses across studies, and these appear in the discussion on overall vaccine efficacy.
  - Analysis of VE against all HPV related EGL (Restricted MITT-2): The overall VE was 48.5% (95% CI: 21.5, 66.8%). Of note, however, is the 1 vaccine recipient (AN 33082) who developed anogenital cancer at Month 24 not associated with a vaccine HPV type.

- Analysis of VE against all HPV related EGL (MITT-3): The overall VE was 31.5% (95% CI: 9.2, 48.5%). The same case of anogenital cancer was included in vaccine cases.
- Impact on EGLs Diagnosed by Clinical Impression:
  - In the restricted MITT-2 population, there was some VE against clinically diagnosed condyloma accuminata, but not against other EGLs. This was true for the MITT-3 population as well.
- Impact on Pap Test abnormalities:
  - In the restricted MITT-2 population, there was some VE against Pap test abnormalities, especially against HSIL (72.1%; 95% CI: 22.1, 91.9%) and ASC-H (55.9%; 95% CI: 7.1, 80.4%).
- Impact on GYN procedures:
  - In the restricted MITT-2 population, there was a 20.2 % reduction in gyn procedures (95% CI: 7.6, 13.2%).
  - In the MITT-3 population, there was an 11.7% reduction in gyn procedures (2.7, 19.8%).
- Efficacy in subjects with infection prior to vaccination:
  - In subjects who were seropositive and/or PCR positive, the incidence of HPV 6, 11, 16, 18 related CIN was somewhat higher in the Gardasil group (4.7) as compared to the placebo group (4.4).
  - In subjects who were PCR positive and seronegative at baseline, the efficacy against HPV 6, 11, 16, 18 related CIN overall was 20.4%, although this was without statistical significance. In this same group, the efficacy against HPV 16, 18 related CIN 2/3 or worse overall was 12.0%, again without statistical significance. In this same group, the overall rates of HPV 6, 11, 16, 18 related EGLs overall were comparable between the vaccine and placebo groups (3.6 in each group).
  - In subjects who were PCR positive and seropositive at baseline, the vaccine efficacy against HPV 6, 11, 16, 18 related CIN overall was -12.5% without statistical significance. In this same group, the vaccine efficacy against HPV 6, 11, 16, 18 related EGLs overall was 14.2%, without statistical significance.
  - In the group that was seropositive and PCR negative, there were no cases of vaccine HPV related CIN or EGL in the Gardasil group as compared to 2 cases of vaccine related CIN and 0 cases of vaccine HPV related EGL in the placebo group.
  - Analyses across trials and further discussion regarding these populations are included in the summary of overall efficacy.

Immunogenicity

- There was no evidence of interference with the immune response to HPV vaccine for all vaccine HPV types when it was given with Hepatitis B vaccine using the prespecified criteria using GMTs or seroconversion.
- There was no evidence of interference with the immune response to Hepatitis B vaccine when it was given with HPV vaccine using the prespecified criteria using seroconversion. Seroconversion is measured by the proportion of subjects who achieve anti-HBs levels $\geq$ 10 mIU/mL at Week 4 postdose 3 Hepatitis B vaccine. As

noted, subjects could be enrolled only if initial anti-HBc and anti-HBs antibodies were negative. (It is noted that the GMTs to Hepatitis B were lower when the vaccines were given concomitantly as compared to when the vaccines were given alone).

- The immune response to the FMP HPV 16 component was non-inferior to PMM HPV 16 vaccine per the prespecified criteria of GMT ratio and seroconersion difference.
- Very few vaccinees did not seroconvert.
- Antibody levels at Month 24 are all higher than levels noted with natural infection.
- Except for HPV 11, subjects who were seropositive and PCR negative had higher GMTs compared to those who were seropositive and PCR positive. This was most apparent at Month 7 and less so a Month 24.
- GMTs were comparable in subjects who were seronegative/PCR negative and seronegative/PCR positive.
- No correlates of protection were identified. There were no breakthrough cases of vaccine type HPV related disease in the PPE poplation. In the MITT-2 population, there were 2 cases CIN and AIS and 3 cases of EGL (each infection developed prior to the 3rd dose).

Safety

- The overall proportion of subjects with one or more AE was somewhat higher in the vaccine recipients compared to placebo recipients.
- The proportion of subjects with injection site AEs in Days 1-5 after each vaccination was higher in vaccine recipients compared to the placebo recipients.
  - The most common injection site AEs were pain, swelling and erythema.
  - Most of the injection site AEs were mild to moderate in severity.
  - There were statistically significant risk differences (higher in vaccine recipients as compared to placebo recipients) for erythema, pain, swelling and burning.
  - There was no apparent difference in the safety profiles between subjects who were seropositive or seronegative at baseline.
- Systemic AEs in Days 1-15 after any injection were comparable between the vaccine and placebo groups.
  - The most common systemic AEs were headache and pyrexia.
  - Incidence rates were comparable in those who were initially naïve and non-naïve to vaccine HPV types.
  - Most systemic AEs were mild to moderate in intensity.
  - 10-15% of systemic AEs were severe, but balanced across vaccinees and placebo recipients.
- SAEs of interest included a subject with bronchospasm 1 day after receipt of dose 3, and facial edema after dose 2, and another subject with worsening asthma. Similar SAEs were noted in vaccinees and placebo recipients.
  - 1 subject had Bell's palsy after receipt of Hepatitis B vaccine (after the Month 18 visit).
  - In the 15 days after vaccination, there was no statistically higher risk of having an SAE in the vaccinees compared to the placebo recipients.
- There were 3 deaths, 2 after receipt of HPV placebo (one due to trauma after receipt of HPV placebo and Hep B vaccine and one due to DVT/PE – this death followed receipt

of HPV placebo and Hep B placebo) and 1 after HPV vaccine (trauma) (which occurred app. 1 year after receipt of the vaccine).

- Pregnancy Outcomes: There were 777 pregnancies in 707 women.
  - There was a somewhat higher proportion of vaccinees who had a spontaneous abortion (93/315=29.5%) compared to placebo recipients (76/289=26.3%). When one additional case is included that was not included in the table provided, the proportion of vaccinees who experienced a spontaneous abortion increased slightly to 29.7% (94/316). The overall rate across trials is presented in the overall summary of safety.
  - Late fetal deaths occurred in 3/315 (0.95%) vaccinees as compared to 0.69% (2/289) of placebo recipients.
  - Of live births, there were 2.7% congenital anomalies in vaccinees (5/187) as compared to 4.1% (7/171) of plaebo recipients.
  - The overall rates of pregnancy outcomes among all the studies and timing of vaccination in these subjects will be discussed overall assessment of safety.

8.1.3 Trial #3

Protocol 007: A Placebo Controlled Dose-Ranging Study of Quadrivalent HPV Virus Like Particle (VLP) Vacine in 16 to 23 Year Old Women
Study Period: 5/26/00 – 5/10/04

This study is reviewed here because efficacy results were combined with efficacy results from Protocols 013 and 015.

Objectives:

- **Part A:** To investigate the general tolerability of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine.
- **Part B:** To identify the formulation with HPV 6, 11, 16, 18 that, when administered IM in a 3 dose regimen, results in acceptable type specific anti-HPV responses, and to demonstrate that the administration of the quadrivalent HPV vaccine is well tolerated.

Design Overview:

- This was a Phase IIb study**.** Part A was a randomized, double blind, placebo controlled, multicenter, sequential dose escalating protocol. Part B was a randomized, double-blind, placebo controlled, multicenter (23 sites in 5 countries: US, Brazil, Finland, Norway, and Sweden), dose ranging study.

TABLE 134
Protocol 007: Vaccination Regimen – Part A

Group	Dose (mcg) HPV 6	HPV 11	HPV 16	HPV 18	Alum	Number of Subjects Targeted to be Enrolled
Ia	0	0	0	0	225	10
Ib	0	0	0	0	450	5
II	20	40	40	20	225	10
III	40	40	40	40	225	10
IV	80	80	40	80	395	10
Total						45

HPV = Human papillomavirus.

Source: Table 5-6, CSR 007, p. 99

TABLE 135
Protocol 007: Vaccination Regimen – Part B

Group	Dose (mcg) HPV 6	HPV 11	HPV 16	HPV 18	Alum	Approximate Number of Subjects to be Enrolled†
Ia	0	0	0	0	225	125
Ib	0	0	0	0	450	125
II	20	40	40	20	225	250
III	40	40	40	40	225	250
IV	80	80	40	80	395	250
Total						~1000

† Assuming an initial 15% sero-/PCR (+) rate for each of HPV 16 and 18, a 40% sero-/PCR (+) rate for HPV 6/11, and a 10% drop-out rate, there were to be at least 134 evaluable subjects per formulation for each HPV type.
HPV = Human papillomavirus; PCR = Polymerase chain reaction.

Source: Table 5-7, CSR 007, p. 100

Population: Healthy women 16-23 years of age. See **APPENDIX 10** for full inclusion and exclusion criteria.

Products Mandated by Protocol

TABLE 136
Protocol 007: Clinical Supplies: Formulation Numbers, Control Numbers, Dosage and Package Information (Part A)

Clinical Material	Formulation Numbers	Control Numbers	Dosage	Package
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI014I001	WP-G861 WP-H563	20/40/40/20 mcg/ 0.5 mL	0.8-mL single-dose vial
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI014J001	WP-G861 WP-H563	40/40/40/40 mcg/ 0.5 mL	0.8-mL single-dose vial
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI015K001	WP-G861 WP-H563	80/80/40/80 mcg/ 0.5 mL	0.8-mL single-dose vial
Placebo (Aluminum Adjuvant)	PV501 VAI013A002	WP-G861 WP-H563	225 mcg/ 0.5 mL	0.8-mL single-dose vial
Placebo (Aluminum Adjuvant)	PV501 VAI012A002	WP-G861 WP-H563	450 mcg/ 0.5 mL	0.8-mL single-dose vial
HPV = Human papillomavirus; VLP = Virus-like particles.				

Source: Table 5-8, CSR 007, p. 101

TABLE 137
Protocol 007: Clinical Supplies: Formulation Numbers, Dosage, and Package Information (Part B)

Clinical Material	Formulation Numbers	Dosage	Package
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI014I001	20/40/40/20 mcg/ 0.5 mL	0.8-mL single-dose vial
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI014J001	40/40/40/40 mcg/ 0.5 mL	0.8-mL single-dose vial
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine	V501 VAI015K001	80/80/40/80 mcg/ 0.5 mL	0.8-mL single-dose vial
Placebo (Aluminum Adjuvant)	PV501 VAI013A002	225 mcg/ 0.5 mL	0.8-mL single-dose vial
Placebo (Aluminum Adjuvant)	PV501 VAI012A002	450 mcg/ 0.5 mL	0.8-mL single-dose vial
HPV = Human papillomavirus; VLP = Virus-like particles.			

Source: Table 5-9, CSR 007, p. 102

- It is noted that the 2 lower dose vaccine formulations contained 225 mcg aluminum and the highest dose formulation contained 395 mcg aluminum.

Endpoints

Efficacy Parameters

- External genital and cervicovaginal persistent infection with HPV 6, 11, 16, and/or 18 by PCR.
- Persistent infection was subsequently detected as positive for the same HPV type by the HPV 6, 11, 16, or 18 PCR assay to at least 1 common gene in 2 or more

consecutive cervicovaginal/external genital or biopsy samples obtained at least 4 months apart or demonstrated first time HPV 6, 11, 16, or 18 PCR positivity at the last visit on record (before being lost to follow-up or at the last study visit) without confirmation of persistent HPV infection.

Secondary Efficacy Endpoint

- With the implementation of Protocol Amendment 007-04, a secondary objective was added to the protocol to evaluate the efficacy of the quadrivalent HPV L1 VLP vaccine with respect to the composite endpoint of persistent HPV 6, 11, 16, or 18 infection or HPV 6-, 11-, 16-, or 18-related genital disease (Cervical, Vaginal, or Vulvar Intraepithelial Neoplasia or related cancers, AIS, and Genital Warts).
- A biopsy showing pathologic evidence of HPV disease as determined by the consensus diagnosis of the Pathology Panel could be classified as a case of persistent infection according to Tables 138 and 139 (reproduced below).

TABLE 138
Protocol 007

Case Definitions of Persistent Infection for Subjects Who Had Biopsies Showing Pathologic Evidence of HPV Disease (as Defined by the Consensus Diagnosis of the Pathology Panel) and Who Had Not Had Definitive Therapy Performed

Sample/Test	Scenario							
	1	2	3	4	5	6	7	8
Cervicovaginal/external genital swab obtained at visit immediately prior to biopsy—test for HPV 6, 11, 16, or 18 by PCR	+	+/–	–	+	+/–	–	–	+
Biopsy (frozen adjacent tissue)—test for HPV 6, 11, 16, or 18 by PCR	+	+	+	N/A†	N/A†	N/A†	N/A†	–
Biopsy swab—test for HPV 6, 11, 16, or 18 by PCR	N/A†	N/A†	N/A†	+	+	+	–	–
Cervicovaginal/external genital swab obtained at visit immediately following biopsy—test for HPV 6, 11, 16, or 18 by PCR	+/–	+	–	+/–	+	–	–	+
Case Definition	Case‡	Case‡	Noncase	Case§	Case§	Noncase	Noncase	Case§

† N/A = The biopsy swab was only considered in the case definition if biopsy tissue was unavailable for PCR.
‡ For these cases, if the biopsy sample showed evidence of disease (as defined by the consensus diagnosis of the Pathology Panel), then the time interval between the biopsy sample and the previous or next positive sample could have been <4 months. If the biopsy sample did not show evidence of disease (as defined by the consensus diagnosis of the Pathology Panel), then the subject was a case only if 2 consecutive specimens taken at least 4 months apart were positive for the same HPV type (6, 11, 16, or 18).
§ Case = This was a case as long as any 2 of the HPV 6, 11, 16, or 18 PCR-positive samples were at least 4 months apart.
HPV = Human papillomavirus.
PCR = Polymerase chain reaction.

Source: Table 5-3, CSR 007, p. 86

TABLE 139
Protocol 007

Case Definitions of Persistent Infection for Subjects Who Had Biopsies Showing Pathologic Evidence of HPV Disease (as Defined by the Consensus Diagnosis of the Pathology Panel) and Who Had Definitive Therapy Performed

Sample/Test	Scenario										
	1	2	3	4	5	6	7	8	9	10	11
Cervicovaginal/external genital swab obtained at visit immediately prior to biopsy—test for HPV 6, 11, 16, or 18 by PCR	+	+	+/–	–	–	+	+/–	+	+	+/–	+
Biopsy (frozen adjacent tissue)—test for HPV 6, 11, 16, or 18 by PCR	+	+/– or N/A†	+	+	–	N/A†	N/A†	N/A†	+	+	– or N/A†
Biopsy swab—test for HPV 6, 11, 16, or 18 by PCR	N/A†	N/A†	N/A†	N/A†	N/A†	+/–	+	+	N/A†	N/A†	N/A†
Biopsy obtained at definitive therapy—test for HPV 6, 11, 16, or 18 by PCR	+/–	+	+	–	+	+	+	–	N/A†	N/A†	N/A†
Biopsy swab obtained at definitive therapy—test for HPV 6, 11, 16, or 18 by PCR	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	+/–	+	+
Case definition	Case‡	Case‡	Case‡	Noncase	Noncase	Case‡	Case‡	Case§	Case‡	Case‡	Case§

† N/A = The biopsy swab was only considered in the case definition if biopsy tissue was unavailable for PCR. In rare cases, both biopsy tissue and the biopsy swab may have been unavailable (see Scenarios 2 and 11).

‡ For these cases, if the biopsy sample showed evidence of disease (as defined by the consensus diagnosis of the Pathology Panel), then the time interval between the biopsy sample and the previous or next positive sample could have been <4 months. If the biopsy sample did not show evidence of disease (as defined by the consensus diagnosis of the Pathology Panel), then the subject was a case only if 2 consecutive specimens taken at least 4 months apart were positive for the same HPV type (6/11/16/18).

§ Case = This was a case as long as any 2 of the HPV 6, 11, 16, or 18 PCR-positive samples were at least 4 months apart.

If the only samples available for a subject were the cervicovaginal/external genital swabs and biopsy swabs (i.e., the subject had no tissue available from any biopsy), the subject was a case only if 2 consecutive specimens taken at least 4 months apart were positive for the same HPV type (6, 11, 16, or 18).

HPV = Human papillomavirus.

PCR = Polymerase chain reaction.

Source: Table 5-4, CSR 007, p. 873

Other Exploratory Efficacy Parameters:

- The incidence of invasive HPV-related procedures (colposcopy with biopsy, definitive therapy, genital warts excision)
- The exploratory parameters regarding potential therapeutic efficacy included: the rate of clearance of HPV 6, 11, 16, or 18 infection; the time to clearance of infection; and the rate of progression to clinically apparent HPV 6-, 11-, 16-, or 18- related disease

Immunogenicity Response Parameters

- The immunogenicity endpoints were changed when the assay was changed to the cLIA method in Protocol amendment 007-06. (See Appendix 16 for reasons for the change in assay.)
- The original primary objective of Protocol 007 was to select a dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine for use in Phase III studies. The dose for Phase III (20/40/40/20 mcg) was selected in June 2001 based on an interim analysis using approximately 50% of the Postdose 3 anti-HPV 6, 11, 16, and 18 cRIA responses.

Safety Parameters

- The primary variables of interest were the proportion of subjects with severe injection site adverse event and the proportion of subjects with any vaccine related serious adverse events.

Protocol 007 Surveillance

TABLE 140

Protocol 007: Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Day 1	Mo 2	Mo 3	Mo 6	Mo 7	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36
Consent	+									
Gyn Hx	+				+	+		+		+
Gyn PE	+				+	+		+		+
Lab:										
Pregnancy test (a)	+	+		+						
Urine GC (PCR or LCR or SDA)	+				+	+		+		+
Urine chlamydia (PCR or LCR or SDA)	+				+	+		+		+
Lab (b)										
Anti-HPV (6,11,16,18) cLIA	+	+	+	+	+	+	+	+	+	+
HPV Assay standard development					+					+
---------- swabs	+				+	+	+	+	+	+
---------- swab for HPV PCR	+				+	+	+	+	+	+
Swab for HSV culture (if indicated)	+				+	+	+	+	+	+
Ph Vag fluid (opt)	+				+	+		+		+
Wet mount/trich/BV(opt)	+				+	+		+		+
Whiff test BV (opt)	+				+	+		+		+
KOH for yeast (opt)	+				+	+		+		+
---------- swab	+				+	+	+	+	+	+
Pap test (Thin Prep) cyto	+				+	+	+	+	+	+
Genital Wart Inspection						+	+	+	+	+
Colposcopy										+
Vaccination (c)	+	+		+						
Clin f/u for safety (d)	+	+	+	+	+					
Questionnaire (e)	+									+

a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)

b. Serum for Ab may be after gyn exam, before vaccination (MRL)

c. Temp and wt prior to each vaccination

d. Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. For Part A only: Four days after each subject received the first vaccination (Day 1), the site contacted each subject to establish the absence of vaccine attributable SAEs and assessgeneral safety. After app. 15 subjects in a formulation group had been contacted, the sponsor established general safety and notified the sites to proceed to the next dose formulation. 14 days after the last vaccination in the last sequential formulation group, and after the sponsor established general safety, the sponsor notified the sites to proceed to Part B. At Months 2, 3, and 7, the study personnel together with the participant reviewed the VRC. At Months 2, 3, 6, and 7, subjects were solicited for any gyn health concerns and any SAEs.

e. All subjects received a self-administered questionnaire at Day 1 and either Month 36 or at early withdrawal.

*cLIA: Competitive immunoassays developed by MRL using technology from the Luminex Corporation, Austin, TX, USA. Source: Table 5-5, CSR 007, p. 91-2

- Procedures were as noted above in the schedule of clinical observations.
- Safety follow-up is as noted in the Detailed Safety Follow-up in Protocol 015.
- Pregnancies which occurred through Month 7 were to be followed for outcome.
- A colposcopy triage algorithm was followed (although were noted to be guidelines, not mandatory). See **APPENDIX 11.**
  Reviewer's Comment: The algorithm is similar to the triage plan used in Study 013.

Statistical Considerations

Efficacy Objective

- The secondary objective was to evaluate the efficacy of the quadrivalent HPV vaccine with respect to the composite endpoint of persistent HPV 6, 11, 16, or 18 infection or HPV 6-, 11-, 16-, or 18-related genital disease (Cervical, Vaginal, or Vulvar Intraepithelial Neoplasia or related cancers, Adenocarcinoma in Situ [AIS], and Genital Warts). This objective was addressed through the Secondary Hypothesis that stated the 20/40/40/20-mcg dose of quadrivalent HPV vaccine reduces the combined incidence of persistent HPV 6, 11, 16, or 18 infection or HPV 6-, 11-, 16-, or 18-related genital disease (Cervical, Vaginal, or Vulvar Intraepithelial Neoplasia or related cancers, Adenocarcinoma in Situ [AIS], and Genital Warts) compared with placebo (including 225 mcg or 450 mcg aluminum adjuvant placebos). Only subjects enrolled in the dose-ranging phase (Part B) were evaluated for this objective.
- The secondary hypothesis to address efficacy was added after enrollment was complete. A total of 20 cases of composite endpoint of persistent infection or diseases related to the vaccine HPV types were required to have 89.8% power to declare the vaccine efficacious with a 2-sided alpha = 0.05, assuming a true VE of 80%.

Efficacy Analysis Populations

- The efficacy populations are as defined in Protocols 015 and 013.

Handling of Dropouts or Missing Data: When data that were needed to establish a subject's eligibility for analysis were missing, the following rules applied:

- Subjects who were missing a baseline cLIA result for a particular vaccine HPV type were not eligible to be classified as cases of infection or disease endpoints related to that HPV type.
- With respect to missing PCR results for external genital/cervicovaginal specimens, a subject's eligibility for analysis depended on the number of missing results. The PCR results for 1 external genital and 2 cervicovaginal specimens collected at each of Day 1 and Month 7 were used to determine each subject's eligibility for analysis. For a given vaccine HPV type, subjects with missing PCR results for 2 or 3 of the 3 specimens at enrollment or Month 7 were not eligible to be classified as cases of infection or disease related to that HPV type. Subjects missing 1 of the 3 PCR results at enrollment and/or Month 7 were eligible. In this situation, if either of the 2 results present for the given HPV type was positive, the subject was considered positive. If both were negative, the subject was considered negative. Missing data that resulted from a subject dropping out of the study was treated as missing (non-existent) in the efficacy analysis.

Counting of Cases of vaccine-HPV-type-related external genital warts, VIN, VaIN, CIN, AIS, and cancer:

- If a subject had a biopsy, excised tissue from an external genital lesion or wart, ECC specimen, or definitive cervical therapy specimen collected during the efficacy evaluation phase, and the PCR result or Pathology Panel diagnosis was missing for the specimen, then the subject could not be classified as a case based on that specimen.
- Subjects who had definitive therapy performed were censored from the efficacy analyses on the date of definitive therapy (because such therapy removes a substantial piece of the cervix, and it is not clear how such a procedure impacts a subject's subsequent risk of cervical disease.)
- A sensitivity analysis was performed in which the endpoint definition was based on the more severe of the central laboratory or Pathology Panel diagnosis of each biopsy.

Immunogenicity Objectives

- The primary immunogenicity objective of the study was to identify formulations of HPV 6, 11, 16, and 18 VLPs that, when administered by intramuscular injection in a 3-dose regimen, result in acceptable type-specific anti-HPV responses.
  - This objective was addressed in a separate report by a test of the Primary Hypothesis which states that for one or more formulations, the quadrivalent HPV vaccine will be immunogenic with respect to each of the components individually at Week 4 Postdose 3 in an acceptable percentage of subjects who were seronegative (Day 1) and PCR-negative (Day 1 through Month 7).
  - For Part A, immunogenic was defined as anti-HPV 6, 11, 16 and 18 cRIA ≥200 mMU/mL. The hypothesis was tested in an interim analysis when approximately 50% of Postdose 3 (Month 7) cRIA responses were available for subjects enrolled in Part B (Dose-Ranging Phase) of the study. It was concluded during the interim analysis that all active dose formulations of quadrivalent HPV vaccine were immunogenic. The 20/40/40/20-mcg dose of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine was selected as the final dose for evaluation in Phase III studies. Approximately 134 evaluable initially seronegative/PCR-negative (Day 1 through Month 7) subjects for each vaccine component per active dose were required for the analysis.
  - The revised immunogenicity endpoints were: (1) anti-HPV 6, 11, 16, and 18 serum cLIA levels at Months 0, 2, 3, 6, 7, 12, 18, 24, 30 and 36; and (2) anti-HPV 6, 11, 16 and 18 serum cRIA levels at all available time points.

Immunogenicity Populations

TABLE 141
Protocol 007: Definitions of Immunogenicity Populations

Efficacy Population	Definition
Per Protocol Imunogenicity Population	*Received all 3 vaccinations *Sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Did not deviate from protocol
All Type Specific HPV Naïve Subjects with Serology Data Population	*Sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV type *Had a valid serology result after the 3rd vaccination *Included protocol violators
All Baseline Type Specific HPV seropositive Subjects	*Included all subjects who were serospositive to the appropriate vaccine component at Day 1 *Included protocol violators

Safety Evaluation

- **Part A (Dose Escalation Phase):** The primary safety objective for Part A was to investigate the general tolerability of the quadrivalent HPV vaccine. This objective was addressed by monitoring safety data for serious adverse experiences between dose stages.
- **Part B (Dose-Ranging Phase):** The primary safety objective in Part B was to demonstrate that the administration of quadrivalent HPV vaccine is generally well tolerated.

Safety Population

- All subjects who received at least one injection and had follow-up data were included in the safety summary.

Primary Safety Endpoint

- The primary endpoint for safety was the proportion of subjects with serious vaccine-related adverse experiences.

Placebo Doses

- Due to differing concentrations of aluminum in the various vaccine and placebo treatment groups, subjects who received the lower doses of qaudraivalent vaccine formulation were primarily compared with subjects who received placebo with 225 mcg aluminum per dose.
- Subjects who received the highest dose formulation were compared with subjects who receibed placebo with 450 mcg aluminum per dose.
- The safety profiles of the 2 placebo groups were to be compared observationally. If their safety profiles appeared similar, then the 2 placebo groups were to be combined for comparing with each of the 3 quadrivalent HPV vaccine groups instead of the separate comparisons mentioned above.

Interim Analysis

- An interim safety analysis was conducted to evaluate adverse experience data that were accrued from the time of initiation of Part A until 2 weeks following enrollment of app. 45 subjects into Part A of the study.
- The safety data from Part A of the study underwent clinical review prior to the initiation of Part B of the study. In order to ensure that no safety problems were occurring with the quadrivalent HPV vaccine, safety was monitored during Part B of the study by an independent Safety Monitor who determined if any actions should be taken based on the data.
- At the following 3 time points during the study: (1) after 50% of the subjects in Part B had received Dose 1, (2) after 50% of the subjects in Part B had received Dose 2, and (3) after 50% of the subjects in Part B had received Dose 3, all available safety data were summarized by an unblinded Merck statistician who was not otherwise associated with the HPV Vaccine program and sent to the Safety Monitor. Summaries were also provided in the event that there was a specific safety concern during the study.
- Additionally, at the time that app. 50% of the Postdose 3 (Month 7) responses from Part B were available, an administrative interim analysis was conducted on the Postdose 3 responses in order to assist in choosing a dose for future studies.
- Part B of Protocol 007 was a double-blinded study, operating under in-house blinding procedures. The interim analysis was performed by an unblinded Merck statistician not otherwise associated with the HPV Vaccine program. The unblinded statistician provided the results of the interim analysis to a dose selection committee that was responsible for reviewing the results and selecting a dose for future studies. The results of this administrative look remained confidential to investigators until the initiation of the Phase III clinical program. At that time, the investigators participating in the Protocol 007 knew what dose was selected for evaluation in Phase III, but did not know the individual vaccination assignments of the subjects in the study.

Changes in Protocol and Changes in Statistical Analyses: Six amendments to the protocol submitted to the IND and reviewed prior to unblinding. Several changes in statistical analyses were also noted and did not impact on primary efficacy and safety evaluations. See **APPENDIX 12** for details**.**

Results

Populations Enrolled/Analyzed

- A total of 1106 subjects were enrolled into the dose ranging study (Part B). Of the 1106 subjects randomized, 3 subjects (AN 7263, 7322, and 9530) were not vaccinated. Of the 1106 subjects randomized, 958 completed the entire 3-year study period.
- 6.9% discontinued during the vaccination period. The most common reason was withdrawal of consent, the majority of which were for relocation or personal issues.
- The proportions of subjects who discontinued the study were comparable among vaccination groups.
- Regional populations: There were 501 subjects from the US, 372 subjects from Brazil, and 233 subjects from the Nordic countries.
- The subject disposition of the Dose Ranging Phase is provided in Table 142 below.

TABLE 142
Protocol 007: Subject Disposition (Part B, Dose Ranging Phase)

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV 6, 11, 16, 18 Vaccine			
	225 mcg	450 mcg	20/40/40/20 mcg	40/40/40/40 mcg	80/80/40/80 mcg	Total
Screened but not enrolled (failure to meet I/E criteria)						0
Randomized	135	140	277	274	280	1106
Vaccinated at:						
Dose 1	135 (100%)	140 (100%)	276 (99.6%)	272 (99.3%)	280 (100%)	1103 (99.7%)
Dose 2	130 (96.3%)	137 (97.9%)	267 (96.4%)	264 (96.4%)	274 (97.9%)	1072 (96.9%)
Dose 3	127 (94.1%)	135 (96.4%)	259 (93.5%)	253 (92.3%)	261 (93.2%)	1035 (93.6%)
Vaccination Period (Day 1 through Month 7)						
Entered	135	140	276	272	280	1103
Completed	126 (93.3%)	134 (95.7%)	256 (92.8%)	251 (92.3%)	260 (92.9%)	1027 (93.1%)
Discontinued	9 (6.7%)	6 (4.3%	20 (7.2%)	21 (7.7%)	20 (7.1%)	76 (6.9%)
Without Long Term Follow-up	9 (6.7%)	6 (4.3%)	20 (7.2%)	21 (7.7%)	20 (7.1%)	76 (6.9%)
Clinical AE	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	3 (0.3%)
Lost to follow-up	3 (2.2%)	0 (0.0%)	4 (1.4%)	6 (2.2%)	5 (1.8%)	18 (1.6%)
Other Reasons	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)
Pregnancy	1 (0.7%)	1 (0.7%)	3 (1.1%)	1 (0.4%)	3 (1.1%)	9 (0.8%)
Protocol deviations	1 (0.7%)	2 (1.4%)	1 (0.4%)	2 (0.7%)	0 (0.0%)	6 (0.5%)
Withdrew consent	4 (3.0%)	2 (1.4%)	12 (4.3%)	9 (3.3%)	12 (4.3%)	39 (3.5%)
Long Term Follow-up Period (> Month 7)						
Entered	126	134	256	251	260	1027
Completed	116 (92.1%)	126 (94.0%)	239 (93.4%)	236 (94.0%)	241 (92.7%)	958 (93.3%)
Discontinued	10 (7.9%)	8 (6.0%)	17 (6.6%)	15 (6.0%)	19 (7.3%)	69 (6.7%)
Lost to follow-up	4 (3.2%)	3 (2.2%)	6 (2.3%)	8 (3.2%)	5 (1.9%)	26 (2.5%)
Moved	2 (1.6%)	0 (0.0%)	2 (0.8%)	2 (0.8%)	1 (0.4%)	7 (0.7%)
Other reason	0 (0.0%)	1 (0.7%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	3 (0.3%)
Protocol deviations	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	2 (0.2%)
Withdrew consent	4 (3.2%)	4 (3.0%)	7 (2.7%)	4 (1.6%)	12 (4.6%)	31 (3.0%)

Source: Table 6-1, CSR 007, p. 154-5

- In the dose escalation phase of the study (Part A), 83.2% (450 mcg alum placebo) - 100% of each group completed the vaccination phase. This part of the trial involved small numbers of subjects. (Source: Table 11-115, CSR 007, p. 750-1, not shown here)

Efficacy and Immunogenicity Populations Analyzed

- The primary analysis of efficacy and immunogenicity were based on the analysis specific per protocol populations from Part B of the study.
- The reasons for exclusion from each of the per-protocol populations from the PPE and PPI analyses are presented in Table 143 below, along with reasons for exclusion from the MITT efficacy populations. Only the subjects who received the 20/40/40/20 dose of the vaccine are included in Table 143 below (both alum doses together).
- Baseline serostatus was determined by the cLIA test.

TABLE 143
Protocol 007: Subject Accounting for the PPE Efficacy and Immunogenicity Populations (Part B)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (20/40/40/20 mcg) (N=277)	Placebo† (N=275)	Total (N=552)
Number of Subjects who received at least 1 injection	**276**	**275**	**551**
Excluded From Per-Protocol Efficacy Population			
HPV 6/11	59	61	120
HPV 16	75	72	147
HPV 18	49	46	95
Included in Per-Protocol Efficacy Population			
HPV 6/11	217	214	431
HPV 16	201	203	404
HPV 18	227	229	456
Excluded From Per-Protocol Immunogenicity Population			
HPV 6/11	68	77	145
HPV 16	82	90	172
HPV 18	57	66	123
Included in Per-Protocol Immunogenicity Population			
HPV 6/11	208	198	406
HPV 16	194	185	379
HPV 18	219	209	428

Source: From Table 6-2, CSR 007, p.157-8

- The most common reason for exclusion was evidence of prior exposure to the relevant HPV type (HPV 6/11, 16, 18) (seropositive at Day 1 or PCR positive on or before Month 7). The reasons for exclusion were generally balanced between the placebo and active vaccine group.

Demographics

- Mean age: 20 years.
- Ethnic Distributions: Caucasians (78.1%), with 9.1% Black, 5.2% Hispanic American, 3.7% other, 3% Asian and 0.8% Native American.
- Smoking status: Overall, 62.7% never smoked, and 25% were current smokers.
- The demographic characteristics of subjects in each of the treatment groups were similar. (Source: Table 6-4, CSR 007, p. 163, not shown here).
- The demographic data for subjects who were initially HPV positive at baseline, and these data were comparable to the overall cohort. (Source: Table 11-26, CSR 007, p. 475-6, not shown here)

Sexual Demographics

- The mean age at first sexual intercourse was between 16 and 17 for each vaccination group.

- Over 60% of subjects reported fewer than 3 lifetime sexual partners at enrollment. Most of these female subjects had 0 or 1 new male sexual partner in the past 6 months prior to the study.
- Overall, sexual histories were comparable among the 5 vaccination groups. (Source: Table 6-5, CSR 007, p. 168, not shown here)
- The subjects in Brazil had a slightly younger age of sexual debut (15.9 years).
- There were a higher percentage of subjects in the Nordic countries with 4 lifetime male sexual partners compared to the other two regions.
- The percentage of subjects in the US with new sexual partners within the last 6 months was somewhat lower compared to the other two regions. (Source: Tables 11-7, 11-8, 11-9, CSR 007, p. 446-51, not shown here)

Gynecologic History

- Overall, 13% of subjects reported a previous history of cervicovaginal infection or sexually transmitted diseases (STDs). The most common infections reported were vaginal candidiasis and bacterial vaginosis.
- The overall incidences of the non-HPV cervicovaginal infections and STDs listed were generally comparable among vaccination groups, both in the overall study cohort and in the PPE population. (Source: Table 6-6, CSR 007, p. 169, and Table 11-10, p. 452, not shown here)
- The overall incidences of such infections and diseases were comparable among the 3 study regions. (Source: Tables 11-11, 11-12, 11-13, CSR 007, p. 453-5)

Non-HPV cervicovaginal infections and STDs at Day 1

- The overall prevalence rates of non-HPV cervicovaginal infections and STDs were similar in the overall study cohort and the PPE cohort. (Source: Table 6-7, CSR 007, p. 170, and Table 11-14, CSR 007, p. 456, not shown here)
- The prevalence rates of chlamydia and gonorrhea were higher in Brazilian subjects than in subjects recruited in the other 2 regions, as were the prevalence rates of bacterial vaginosis and trichomonas. (Source: Tables 11-15, 11-16, 11-17, CSR 007, p. 457-9, not shown here)

Pregnancy

- The percentages of subjects that reported a history of pregnancy at enrollment by vaccination group were comparable among the 5 vaccination groups for both the overall cohort and the PPE analysis population. (Source: Table 6-9, CSR 007, p. 171 and Table 11-18, CRS 007, p. 460-1, not shown here)

Contraception

- The most common contraceptive methods were oral hormonal contraceptives and male condom.

HPV Related Pathology at Day 1

- Of the 1072 subjects who were in the dose-ranging phase and had a Day 1 Pap result, 123 (11.6%) subjects had abnormal Pap test results (SIL present) at Day 1.
- In general, the percentages of subjects that had abnormal Pap test diagnoses were comparable among the 5 vaccination groups. Approximately equal numbers of

subjects were diagnosed as ASC-US (5.5% overall) and LSIL (5.4% overall). (Source: Table 6-10, CSR 007, p. 175-6, not shown here)

Anti-HPV Serostatus and HPV PCR Status at Day 1

- Seropositivity was more prevalent than PCR positivity.
- For HPV 6, 6.6% were seropositive; for HPV 11, 2.3% were seropositive; for HPV 16, 10.5% were seropositive; and for HPV 18, 4.2% were seropositive.
- An overall seropositivity rate for all 4 vaccine HPV types together was not provided in the CSR. (Source: Table 6-11, CSR 007, p. 178, not shown here)
- A total of 967/1100 (87.9%) subjects tested PCR negative to all vaccine HPV types at Day 1 and 133/1100 (12.1%) were PCR positive to at least one of the vaccine HPV types.
- More subjects were PCR positive at Day 1 to HPV 16 (8.2%) than to other vaccine HPV types (2.7% for HPV 6, 1.8% for HPV 18, and 1.1% for HPV 11).
- The percentage of subjects who were PCR positive at baseline were generally comparable among the 5 groups, (although the percentage of subjects in the 80/80/40/80 group who were PCR 16 positive [6.1%] was slightly lower than the percentages seen overall [8.2%], although that group [and the 40/40/40/40 group] had a slightly higher percentage of subjects with PCR 18 positive [2.2%] compared to the percentage overall [1.8%]). (Source: Table 6-12, CSR 007, p. 181, not shown here)
- The percentages of subjects with at least 2 vaccine HPV types detected by PCR in any group were very small in each group (overall, 1.6%), and only 1 subject was positive for 3 vaccine types. (Source: Table 6-13, CSR 007, p. 183-4, not shown here)

Prior medications

- The most common medication administered within 3 days prior to vaccination was hormonal contraceptives for all 3 visits. (Source: Table 6-14, CSR 007, p. 186-7, and Tables 11-42 and 11-43, p. 495-8, not shown here).

Concomitant medications

- The most commonly used medications taken from Days 1-15 after any vaccination visit included hormonal contraceptives (75.0%-82.2%), vitamins (10.4%-15.2%), anti-bacterials (14.1%-22.9%), analgesics (30.8%-39.3%), and anti-inflammatory meds (27.6%-32.6%).
- Antihistamines were used in 8.6%-10.5% in this time period. (Source: Table 6-15, CSR 007, p. 189-94)

Medical History

- In general, the medical history prior to vaccination was comparable among the 5 groups.
- The most common medical histories reported were complaints related to the gynecological system, such as dysmenorrhea and vaginal discharge; nervous system disorders such as headache/migraine; skin disorders such as acne; immune system disorders such as seasonal allergies; and GI disorders such as lower abdominal pain. (Source: Table 6-17, CSR 007, p. 197-202, not shown here)

Measures of Treatment Compliance

- The distribution of times of completion of the 2nd and 3rd vaccinations was similar for the vaccine and placebo groups. (Source: Figures 6-2 and 6-3, CSR 007, p. 204-5, not shown here).
- The proportions of subjects completing each of the follow-up visits were comparable among the 5 groups, and ranged from app. 86-88% at Month 36 to app. 92-94% at Month 7. (Source: Table 6-18, CSR 007, p. 206)
- Baseline characteristics of those who discontinued from the study were generally comparable between the groups. Most discontinued due to consent withdrawal, followed by loss to follow-up. (Source: Table 11-54, CSR 007, p. 565, not shown here)

Efficacy

- Efficacy was a secondary objective of the study. The sponsor's "main" efficacy objective was to evaluate the quadrivalent HPV vaccine in prevention of vaccine type related infection or disease among women who were naïve for the vaccine HPV type in question (seronegative at Day 1 and PCR negative Day 1 through Month 7). A 95% CI with a LB > 0% would support this conclusion.
- **Persistent infection** was categorized as follows:
  - **Category A** is the detection of the same vaccine HPV type on consecutive visits at least 4 months apart.
  - **Category B** is the detection of vaccine HPV type DNA in the same lesion in which disease was detected by the Pathology Panel, together with detection of that same HPV type in the antecedent visit.
  - **Category C** is the detection of vaccine type HPV DNA in a subject's last specimen before becoming lost to follow-up.
- **HPV 6, 11, 16, 18 related genital disease endpoint** was defined as follows: A cervicovaginal biopsy found to have pathologic evidence of CIN, VaIN, VIN, external genital warts, cervical, vulvar or vaginal cancer or AIS as determined by the Pathology Panel [the Pathology Panel in Study 007 included the same pathologists as in Studies 013 and 015; it is noted that Dr. Ronette replaced ---------- 10/00] **AND** positive for vaccine type HPV DNA using the Thinsection PCR assay. The Thinsection PCR was not available at the start of the study. When this was not available, a genital disease endpoint required **all 3** of the following events in a single subject:
  - A cervicovaginal/external genital biopsy diagnosed with CIN, VaIN, VIN, external genital warts, cervical, vulvar, or vaginal cancer, or AIS as determined by the consensus diagnosis of the Pathology Panel AND
  - PCR detection of a vaccine HPV type in an tissue sample obtained from the same lesion, or if such a specimen was not available, in a swab of the biopsy site; AND
  - Detection of the same HPV type in a swab collected at the visit *immediately prior to* the visit in which the biopsy procedure was performed.
- For the **main efficacy analysis**, cases of persistent infection and genital disease were counted starting after Month 7. The main analysis was conducted in the PPE population.
  - The **estimate of vaccine efficacy** at 2.5 years after completion of the 3 dose regimen was **89.5% [95% CI: 70.7, 97.3%].** Of the 40 HPV 6-, 11-, 16-, or 18-related persistent infection or disease cases, 13 cases (3 in quadrivalent HPV

[Types 6, 11, 16, 18] L1 VLP vaccine recipients and 10 in placebo recipients) were due to detection of HPV 6, 11, 16, or 18 DNA on samples collected on the last visit of record without confirmation of persistent infection. Per protocol, these subjects were counted as cases in the main efficacy analysis because persistence of detection could not be verified.

- The **efficacy of the quadrivalent HPV vaccine appeared comparable with respect to the various vaccine components.**

TABLE 144
Protocol 007: Analysis of Efficacy Against HPV 6, 11, 16, or 18 Related Persistent Infection or Disease (Per protocol Efficacy Population)

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=276				Placebo 225 mcg and 450 mcg alum N=275					
	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 6, 11, 16, or 18 related infection or disease	235	4	566.8	0.7	233	36	536.5	6.7	**89.5%**	70.7, 97.3%
HPV 6 related endpoints	214	0	517.5	0	209	13	501.2	2.6	**100%**	68.2, 100%
HPV 11 related endpoints	214	0	517.5	0	209	3	503.7	0.6	**100%**	<0, 100%
HPV 16 related endpoints	199	3	484.4	0.6	198	21	465.4	4.5	**86.3%**	54, 97.4%
HPV 18 related endpoints	224	1	541.8	0.2	224	9	536.9	1.7	**89.0%**	20.5, 99.7%

Source: Table 7-2, CSR 007, p. 215

- The sponsor presents the baseline characteristics of subjects who became a case of persistent infection. Compared with the overall PPE population, this group tended to be more sexually active prior to enrollment and during the study. (Source: Table 11-55 and 11-56, CSR 007, p. 566-72, not shown here)
- The 4 cases of persistent infection in the vaccine group include the following subjects:
  - **AN 8111** became PCR positive for HPV 18 at Months 12 and 18. At Month 12, she developed ASCUS. Pap tests after these times were negative, and exit colposcopy at Month 36 was negative. This subject had robust anti-HPV 18 antibody levels.
  - **AN 7414** was noted to have HPV 16 DNA at exit colposcopy without lesion. This subject had robust anti-HPV 16 levels.

- **AN 8289** developed ASCUS at Month 18 and LSIL at Month 30. CV specimens were positive for HPV 16 DNA at Months 12 and 36. She did not have a biopsy during the study. This subject had robust anti-HPV 16 levels.
- **AN 8321** developed ASCUS at Month 12 and LSIL at Month 36. CV specimens were positive for HPV 16 PCR at Month 36. Biopsy at exit colposcopy was **negative for pathology** [showed CIN 1 and negative including cellular reactive changes as per path panel, and CIN 1 and CIN 2 as per the medical lab], but contained HPV 16 DNA. She then had a LEEP and vaginal biopsy and had VaIN 1 and CIN 1 as per the Pathology Panel, but was PCR negative. The medical lab diagnosed vaginal condyloma, and CIN 2, CIN 1, AND CIN 2. [3/1/04] This subject had robust anti-HPV 16 levels.

Vaccine efficacy against persistent vaccine type HPV infection for each of the three geographical regions

- In the Nordic region, the VE was 100% (95% CI: 33.8, 100%).
- In the US, the VE was 95.9% (95% CI: 74.3, 99.9%).
- In Brazil, the VE was the lowest at 60.7% (95% CI: < 0, 93.3%). (Source: Table 11-57, CSR 007, p. 576, not shown here) It is unclear as to the reason for this finding, although the numbers of subjects are small. There does not appear to have been a greater exposure to vaccine HPV types in the Brazilian population.

Vaccine Efficacy against HPV 6, 11, 16 or 18 persistent infection or disease in the MITT populations

Efficacy against HPV 6, 11, 16, and/or 18 related disease or infection are shown in Table 145 below. It is noted that the point estimates of vaccine efficacy remain higher (64.5%, 95% CI: 41.7, 79%) than those seen in Stuies 015 and 013 in subjects who were included regardless of baseline vaccine HPV status.

TABLE 145
Protocol 007: Secondary Analysis of Efficacy Against HPV 6, 11, 16, 18 Related Persistent Infection or Disease (Per Protocol and Modified Intent to Treat Populations)

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=276				Placebo 225 mcg and 450 mcg alum N=275						
Population	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI	p-value
Per protocol	235	4	566.8	0.7	233	36	536.5	6.7	**89.5%**	70.7, 97.3%	<0.001
MITT-1	249	4	599.7	0.7	243	36	558.2	6.4	**89.7%**	71.1,97.3%	<0.001
MITT-2	266	6	723.6	0.8	263	48	667.1	7.2	**88.5%**	73, 96%	<0.001
MITT-3	268	23	690.6	3.3	269	61	650.9	9.4	**64.5%**	41.7, 79%	<0.001

Source: Table 7-4, CSR 007, p. 222

- Corresponding point estimates for VE by individual HPV type are also presented. VE in the MITT-3 population is lowest for prevention of the HPV 16 and 18 efficacy endpoints, with point estimates of 60.2% for HPV 16 (95% CI: 28.4, 78.8%) and 54.6% for HPV 18 (95% CI: < 0, 87.6%).
- The VE in all groups in the MITT 1 and MITT 2 populations are all > 80%., although the LB of the 95% CI for HPV 11 endpoints is < 0% (possibly due to the lower number of cases). (Source: Tables 11-59, 11-60, 11-61, CSR 007, p. 578-83, not shown here)

- In the **MITT-2 population** (naïve for the relevant vaccine HPV type at baseline, with cases were counted 30 days following dose 1)**,** there were 2 additional cases of vaccine HPV type related disease:
  - **AN 7265:** This subject had detectable anti-HPV 16 by cLIA at Month 2. She was HPV 16 PCR positive at Months 7, 12, and 18. Her Month 12 and 18 Pap tests showed LSIL. Her cervical biopsy was negative including reactive cellular changes by the pathology panel and her ECC was read as unsatisfactory by the Path Panel, but was positive for HPV 16 DNA. (This specimen was read as CIN on the cervical biopsy and and negative including reactive cellular changes on the ECC by the medical lab) [10/2/01]. Anti-HPV 16 cLIA levels at Months 3, 6, and 7 were substantially higher than those observed among PPI subjects in the persistence phase. (Note: This subject may have acquired HPV 16 around the time of the first vaccination, or had a previous infection.)
  - **AN 8355:** This subject had an enrollment Pap with LSIL. Two biopsy specimens at Month 2 were read as negative including reactive cellular changes by the pathology panel (and read as atypical squamous metaplasia and unsatisfactory by medical lab) [1/17/01]. The specimen was positive for HPV 16 DNA. The subject discontinued from the study. This subject had detectable anti-HPV 16 by cLIA at Month 2, and anti-HPV 16 levels were substantially higher than those observed among PPI subjects in the persistence phase.

Vaccine Efficacy Against HPV 6, 11, 16, and/or 18 Related Infection or Disease of All Dose Formulations Combined

- The point estimate of vaccine efficacy against vaccine HPV type related persistent infection and disease for all formulations used in this study was 87.6% (95% CI: 76.4, 93.8%), and was comparable to the efficacy of the Gardasil formulation. There was a higher incidence of HPV 18 related persistent infection or disease in vaccine recipients of all formulations compared to subjects who received the final formulation (0.5 per 100 person years at risk compared to 0.2 for the Gardasil formulation), and a wider 95% CI (point estimate of efficacy 70.1%, 95% CI: 12.1, 90%). Five of the additional cases were due to detection of HPV 18 PCR before loss to follow-up. (Source: Table 11-62, CSR 007, p. 584-5, not shown here).

Vaccine Efficacy Against HPV 6, 11, 16, and/or 18 Related DNA detection at $\underline{\geq}$ 1 Visit Following the Month 7 Visit

- The point estimate of vaccine efficacy against vaccine type DNA detection at 1 or more visits was lower in the PPE (73.9%, 95% CI: 50.9, 87%) as compared to the study's main endpoint (detection of same vaccine HPV type at 2 or more visits at least

4 months apart). However, the sponsor postulates that detection of vaccine type HPV DNA was related to transient deposition rather than true infection. There were an almost equal number of additional cases added to both the vaccine (9) and placebo (10) groups as compared to the study's primary analysis. (Source: Table 7-6, CSR 07, p. 228, not shown here).

Vaccine Efficacy Against HPV 6, 11, 16, and/or 18 Related Infection at ≥ 2 Time Points or Disease (not necessarily consecutive)

- No new cases were identified when the time points for detection of vaccine type HPV DNA at least 4 months apart were not consecutive. The vaccine point estimate of efficacy and 95% CI are nearly identical to those in the primary analysis (89.4%, 95% CI: 70.5, 97.4%). (Source: Table 7-7. CSR 007, p. 231, not shown here)

Vaccine Efficacy Against HPV 6, 11, 16, and/or 18 Related Infection at ≥ 2 Time Points or Disease (not necessarily 4 months apart)

- When vaccine type HPV DNA was detected at 2 more consecutive time points but not necessarily 4 months apart, there was one additional case in the placebo group as compared to the vaccine group, with a point estimate of efficacy of 89.8% (95% CI: 71.6, 97.4%). (Source: Table 7-7. CSR 007, p. 231, not shown here)

Central lab or Pathology Panel Diagnosis

- When the sponsor included the worse diagnosis from the central lab or pathology panel in the per protocol analysis, they found there were three vaccine type HPV related EGL cases and four vaccine type HPV CIN cases in the placebo group, and no cases in the vaccine recipients. The point estimate of efficacy against vaccine type related disease was 100% (95% CI: 31.4%, 100%). (Source: Table 7-8, CSR 007, p. 233, not shown here) In the MITT-2 population, the point estimate of efficacy was 91.1% (95% CI: 38.7, 99.8%). (Source: Table 11-64, CSR 007, p. 587, not shown here).

Exploratory Analyses of efficacy with respect to HPV 6, 11, 16, 18 related cervical and external genital disease over the 2.5 years of follow-up.

- In the **PPE population**, 6 cases of vaccine HPV type related genital disease developed in the placebo group (3 vaccine HPV type related EGL and 3 vaccine HPV type related CIN) compared to none in the vaccine group. The point estimate for efficacy was 100% (95% CI: 15.9, 100%). (Source: Table 7-12. CSR 007, p. 243, not shown here)
- In the **MITT-2 population**, there were 4 additional cases in the placebo group. The point estimate for efficacy was 100% (95% CI: 56.4%, 100%). (Source: Table 11-67, CSR 007, p. 591-2, not shown here)
- In the **MITT-3 population**, compared with the MITT-2 population, there were 5 additional cases in the placebo group and 3 cases identified in the vaccine group. Overall, there were 15 cases in the placebo group (4 vaccine HPV type related EGL and 12 vaccine HPV type related CIN [note: a subject may have had more than one type of disease], and 3 vaccine HPV type related CIN cases in the vaccine group. The point estimate for efficacy was 80.3% (95% CI: 30.3, 96.3%). (Source: Table 11-68, CSR 007, p. 593-4, not shown here)

Sensitivity analyses for vaccine HPV type related disease using a modified disease definition

- The definition was modified in that a vaccine HPV type could have been detected either in an antecedent or subsequent swab (in addition to having a Pathology panel diagnosis and vaccine type HPV PCR in an adjacent tissue specimen), and analyses were conducted in the PPE and MITT-2 populations. No new cases were noted in either group in the PPE and MITT-2 populations. (Source: Table 7-12, p. 243 and Table 11-67, p. 591-2, CSR 007, not shown here)

Exploratory Analysis of Risk Factors for becoming a main endpoint case – Protocol 007

- In Protocol 007, the sponsor conducted an exploratory analysis for the odds ratio and 95% CI from a logistic regression model that adjusted one-at-a-time for the index baseline covariate (within the **per-protocol placebo population** only).
- Subjects with a history of smoking had higher odds of developing HPV 6-, 11-, 16-, or 18-related persistent infection or genital disease than those without a smoking history (odds ratio 2.62 [95% CI: 1.13, 6.07].
- Subjects who drank 5 or more alcoholic drinks per week, subjects with a younger age at enrollment, Caucasians, and those with a higher lifetime number of sexual partners also tended to have a higher risk of developing the vaccine-type HPVrelated composite endpoint, although the 95% CIs for the odds ratios for these factors did not include 1. (Source: Table 7-13, CSR 007, p. 246, not shown here)

Exploratory Analysis on Impact of Gardasil on Development of any HPV related Cervicovaginal Disease

- The point estimates of vaccine efficacy against cervical and external genital disease **irrespective of HPV type** were provided for the PPE, MITT-2, and MITT-3 populations. These exploratory analyses are of interest.
- Although there was a positive trend for the subjects in each population, statistical significance was not demonstrated for the point estimates in any of these populations. (See Table 146 below).

TABLE 146
Protocol 007: Analysis of Efficacy Against Cervical and External Disease Irrespective of HPV Type (PPE, MITT-2, MITT-3 Populations)

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=276				Placebo 225 mcg and 450 mcg alum N=275					
Population	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Per protocol	238	5	572.7	0.9	239	11	572.0	1.9	**54.6%**	(<0.0, 87.6%)
MITT-2	268	11	723.4	1.5	268	19	719.4	2.6	**42.4%**	(<0.0, 75.2%)
MITT-3	268	18	714.8	2.5	267	27	706.5	3.8	**34.1%**	(<0.0, 65.8%)

Source: Table 7-14, p. 249; Table 11-69, p. 595; Table 11-70, p. 596, CSR 007

End of Study Pap Tests and Colposcopies- Month 36

- In Study 007 (as in Study 005), colposcopies were performed at the end-of-study Month 36) regardless of the prior Pap test results. No vaccine effects of the sensitivity of the Pap test to detect CIN was reported by the sponsor.
- **Pap test Diagnoses:** At the Month 36 visit, fewer subjects in the vaccine group had Pap test results of LSIL compared to placebo recipients, and none of the vaccine recipients had Pap test results of ASC-H. (See Table 147 below).
- **Cervical Biopsy Diagnoses:** At the Month 36 visit, there was a slightly lower proportion of vaccine recipients with an abnormal cervical biopsy compared to placebo recipients. (See Table 148 below).

Table 147
Protocol 007: Month 36 Pap Test Diagnoses

	Quadrivalent HPV (Types 6, 11, 16, 18) Vaccine N=289	Placebo N=292	Total N=581
Subjects with Pap and colposcopy results at Month 36	241	245	486
Month 36 Pap diagnosis			
Negative for SIL	212 (88.0%)	210 (85.7%)	422 (86.8%)
ASC-US HC-II HR Negative	4	1	5
ASC-US HC-II HR Positive	8	8	16
ASC-H	0 (0.0%)	3 (1.2%)	3 (0.6%)
LSIL	16 (6.6%)	22 (9.0%)	38 (7.8%)

*Subjects with $\geq$ 1 Pap are counted once based on most severe grade
Source: Table 5.3.5.3.1:2, Statistical Documentation, p. 14

Table 148
Protocol 007: Month 36 Cervical Biopsy Diagnoses

	Quadrivalent HPV (Types 6, 11, 16, 18) Vaccine N=289	Placebo N=292	Total N=581
Subjects with Pap and colposcopy results at Month 36	241	245	486
Subjects with a Month 36 cervical biopsy	45	52	97
Month 36 cervical biopsy diagnosis*			
Negative	38 (15.8%)	40 (16.3%)	78 (16.0%)
CIN 1	6 (2.5%)	8 (3.3%)	14 (2.9%)
CIN 2	0 (0.0%)	2 (0.8%)	2 (0.4%)
CIN 3	1 (0.4%)	2 (0.8%)	3 (0.6%)

*Among subjects with Pap and Colposcopy results at Month 36
Source: Table 5.3.5.3.1:6, Statistical Documentation, p. 17

Gynecologic Procedures

- When judged observationally, there were only a very slightly lower incidence of procedures in the vaccine group (13.1 per 100 person years at risk) as compared to the placebo group (13.9 per 100 person years at risk) and one more colposcopy in the vaccine group as compared to the placebo group. (Source: Table 7-16, CSR 007, p. 253, not shown here) (Please see discussion of overall efficacy, impact on procedures).

Efficacy in previously PCR positive and/or seropositive subjects

- No efficacy was documented in this subgroup. There were very few cases in either treatment group, although there was no apparent negative impact on clearance of HPV 6 or 16 infection in the seropositive and PCR positive subgroup, nor in the PCR positive and seronegative subgroup. (Source: Table 7-17, p. 256; Table 7-18, p. 258, CSR 007, not shown here). (See overall efficacy section for further discussion on subjects who are seropositive and PCR positive at baseline).

Immunogenicity Endpoints

Primary Dose Selection

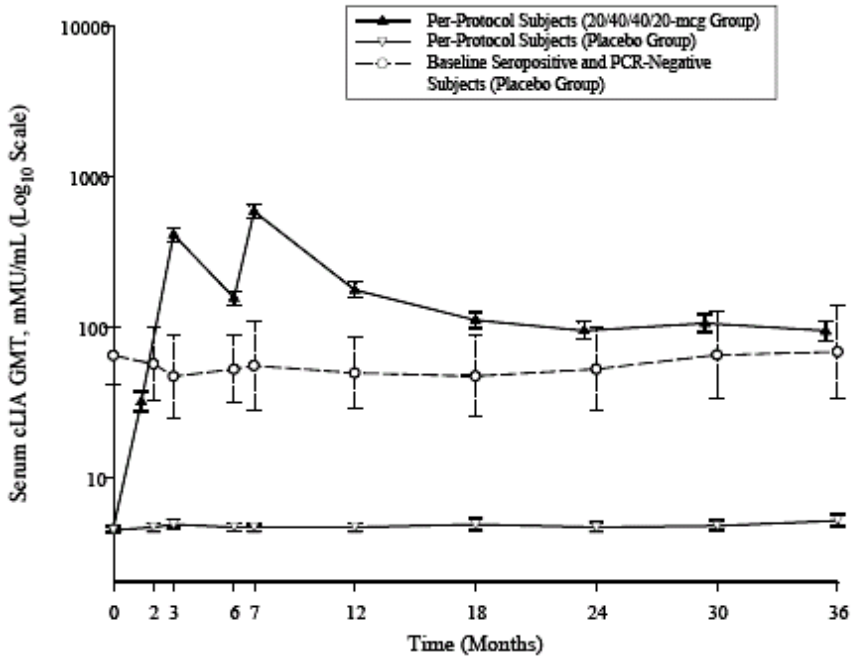
- The primary objective of Protocol 007 was to select a dose for Phase III studies. This dose was based on an interim analysis using app. 50% of the postdose 3 anti-HPV 6, 11, 16, and 18 cRIA responses.
- GMTs at Month 7 across doses, in addition to the percent of subjects with anti-HPV levels $\geq$ 200 mMU/mL at Month 7, are similar within each HPV type. (Source: Figures 7-1 and 7-2, CSR 007, p. 265-6, and Table 7-20, p. 262-4, not shown here)

cLIA results

- In the PPI protocol, for each HPV vaccine type, GMTs increased following each vaccination. In general, the vaccine induced vaccine HPV type responses as early as 4 weeks postdose 2 compared to placebo. These responses are shown in Figures 22-25 below for each vaccine HPV type, and show GMTs through Month 36.

FIGURE 22
Protocol 007

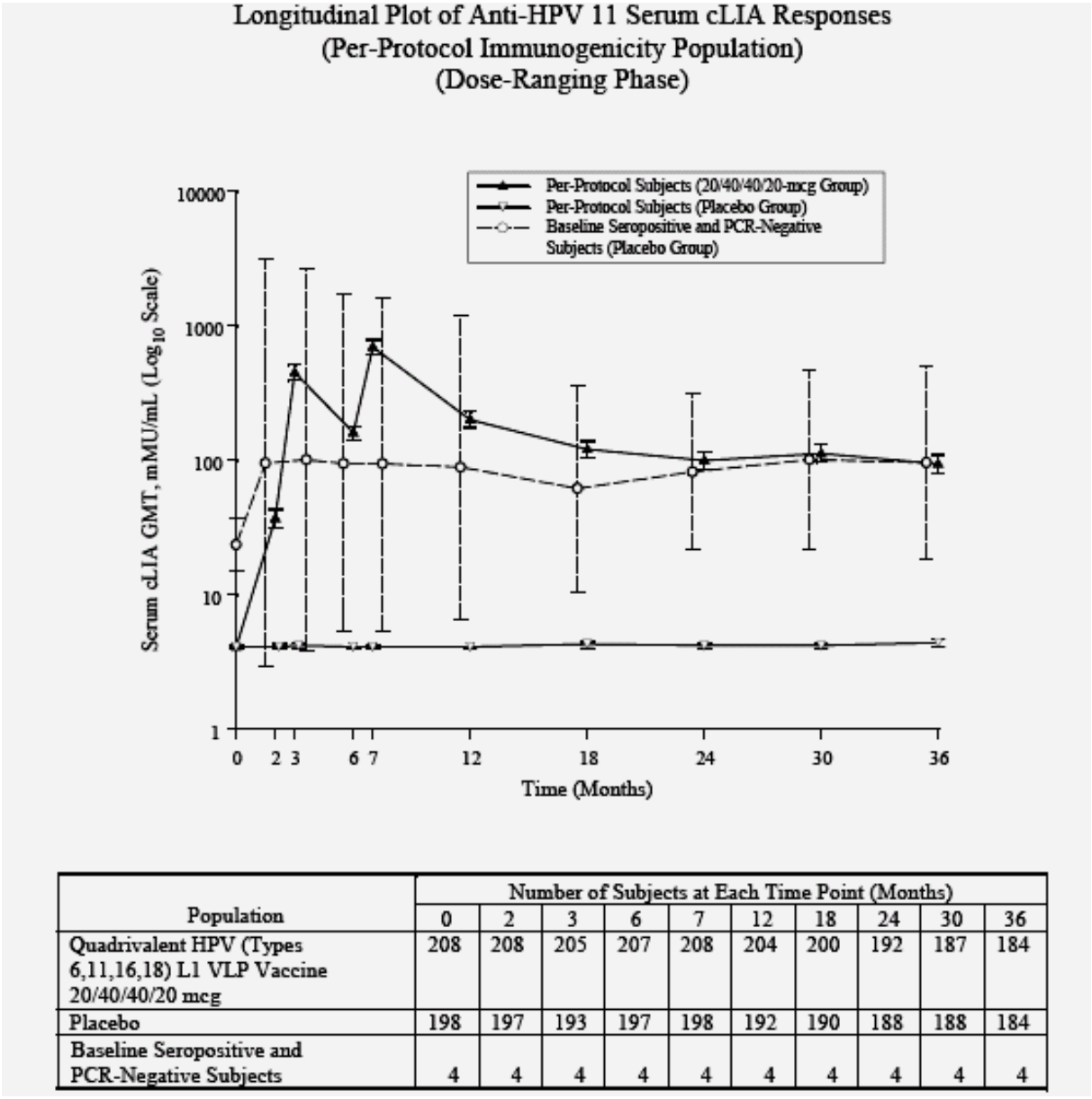
Longitudinal Plot of Anti-HPV 6 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)
(Dose-Ranging Phase)



Population	Number of Subjects at Each Time Point (Months)									
	0	2	3	6	7	12	18	24	30	36
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine 20/40/40/20 mcg	208	208	205	207	208	204	200	192	187	184
Placebo	198	197	193	197	198	192	190	188	188	184
Baseline Seropositive and PCR-Negative Subjects	19	18	17	18	17	18	17	16	16	16

Source: Figure 7-3, CSR 007, p. 274

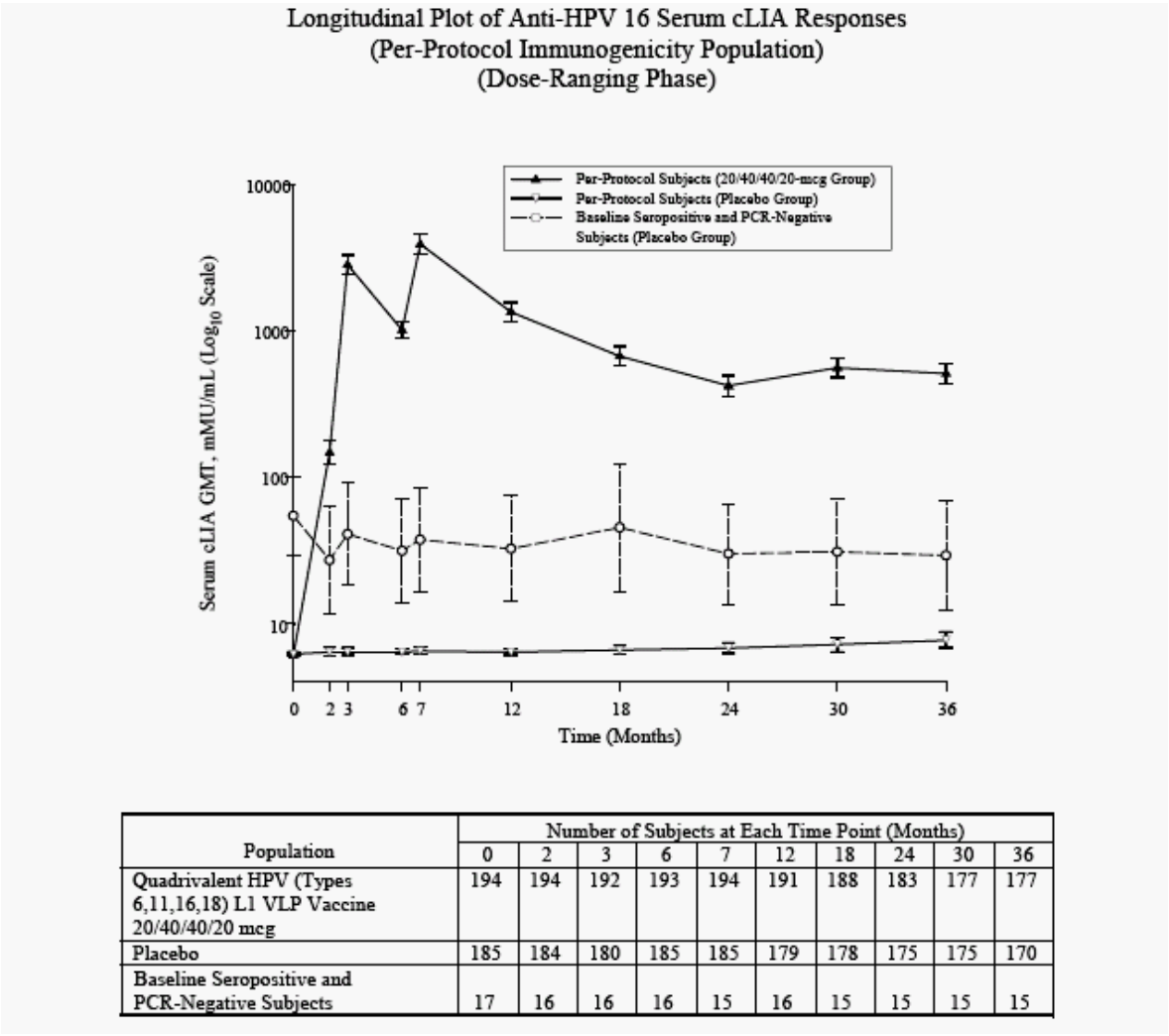
FIGURE 23
Protocol 007



Population	Number of Subjects at Each Time Point (Months)									
	0	2	3	6	7	12	18	24	30	36
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine 20/40/40/20 mcg	208	208	205	207	208	204	200	192	187	184
Placebo	198	197	193	197	198	192	190	188	188	184
Baseline Seropositive and PCR-Negative Subjects	4	4	4	4	4	4	4	4	4	4

Source: Figure 7-4. CSR 007, p. 275

FIGURE 24
Protocol 007

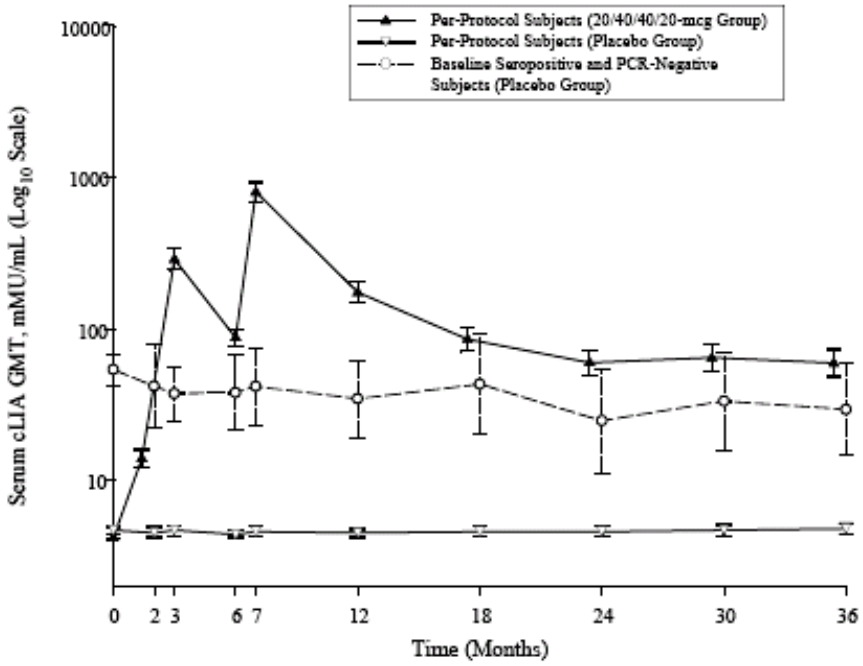


Population	Number of Subjects at Each Time Point (Months)									
	0	2	3	6	7	12	18	24	30	36
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine 20/40/40/20 mcg	194	194	192	193	194	191	188	183	177	177
Placebo	185	184	180	185	185	179	178	175	175	170
Baseline Seropositive and PCR-Negative Subjects	17	16	16	16	15	16	15	15	15	15

Source: Figure 7-5, CSR 007, p. 276

FIGURE 25
Protocol 007

Longitudinal Plot of Anti-HPV 18 Serum cLIA Responses
(Per-Protocol Immunogenicity Population)
(Dose-Ranging Phase)



Population	Number of Subjects at Each Time Point (Months)									
	0	2	3	6	7	12	18	24	30	36
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine 20/40/40/20 mcg	219	219	217	218	219	215	212	204	199	196
Placebo	209	208	204	208	209	203	200	199	198	193
Baseline Seropositive and PCR-Negative Subjects	12	12	11	12	12	12	11	9	10	10

Source: Figure 7-6, CSR 007, p. 277

- Figures for the all naïve with serology population (Figures 11-2, 3, 4, 5, p. 616-9, not shown here) are similar to those for the PPI population.
- The responses were generally comparable among Brazilians, Americans and Europeans, although the Europeans had somewhat lower GMTs as compared to the other groups. (Source: Tables 11-80, 11-81, 11-82, 11-83, CSR 007, p. 620-623, not shown here)
- The SDs of the natural log of anti-HPV 6, 11, 16 and 18 cLIA responses at Month 7 were 0.72, 0.88, 1.11, and 1.08.

Factors that May Affect Month 7 cLIA responses

- In general, for all vaccine types, factors assessed together [race, age < 18 or ≥ 18 years, geographic site, smoking status, prior pregnancy, number of lifetime sexual partners and number of sexual partners within 6 months of vaccination] only accounted for a small proportion (ranging from 6.7 to 10.7%) of the total variation in the log of Month 7 anti-HPV cLIA responses.
- Among the risk factors evaluated, race, smoking history, and number of lifetime partners prior to vaccination accounted for most of the variation.
- Although the number of subjects was small, Hispanics tended to have higher Month 7 anti-HPV GMTs for HPV 6, 11, and 16 than the other race/ethnic groups. There is no apparent clinical impact from these slight variations, although there is a small number of subjects. (Source: Tables 11-80, 11-81, 11-82, 11-83, CSR 007, p. 620-623, not shown here)

Immunogenicity in Previously PCR positive and/or seropositive subjects

- In those who were initially HPV PCR positive and seronegative at Day 1, the GMTs in this group were comparable to those in the PPI group. (Source: Table 7-22, CSR 007, p. 280-1, not shown here)
- In those who were initially HPV PCR negative and seropositive at Day 1, the GMTs were higher at Month 2 (postdose 2) and throughout compared to those who were initially naïve to infection. (Source: Table 7-23, CSR 007, p. 283-4, not shown here)

Exploratory Analysis of Correlates of Protection

- Generally, there were no significant differences between the immune responses in vaccine recipients at at Month 7 who became cases as compared to non-cases for HPV 16. The numbers were small however. (Source: Figure 7-7, CSR 007, p. 286, not shown here)
- For the one vaccine recipient who developed HPV 18 related endpoint of persistent infection (AN 8111), this subject's GMTs were somewhat lower than those of non-cases. In this subject, HPV 18 DNA was detected at Month 12 and 18. (Source: Figure 7-8, CSR 007, p. 287, not shown here)

Safety Outcomes

Summary of Clinical Adverse Events (Days 1-15 after vaccination) (See Table 149 below.)

TABLE 149
Protocol 007: Clinical AE Summary (Days 1-15 following any vaccination visit)
Dose Ranging Study

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV 6, 11, 16, 18 Vaccine		
	225 mcg N=135	450 mcg N=140	20/40/40/20 mcg N=275	40/40/40/40 mcg N=272	80/80/40/80 mcg N=280
Subjects with follow-up	134	140	272	269	277
Subjects with 1+ AE	116 (86.6%)	126 (90.0%)	250 (91.9%)	251 (93.3%)	265 (95.7%)
Subjects with 1+ IS AE	100 (74.6%)	112 (80.0%)	234 (86.0%)	240 (89.2%)	255 (92.1%)
Subjects with 1+ systemic AE	95 (70.9%)	95 (67.9%)	187 (68.8%)	186 (69.1%)	192 (69.3%)
Subjects with SAEs	0 (0.0%)	2 (1.4%)	2 (0.7%)	0 (0.0%)	2 (0.7%)
Subjects who died	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects who discontinued due to AE	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (0.7%)	0 (0.0%)

Source: Table 8-1, CSR 007, P. 299-300

- The proportion of subjects with an AE was slightly higher in the vaccine group as compared to the placebo group.
- **Systemic AEs:** The proportion of subjects with systemic AEs was comparable among the 5 groups.
- **Injection Site AEs:** The proportion of subjects with injection site AEs was somewhat higher in the vaccine group compare with the placebo group. Among the vaccine groups, there was a slight dose response with regard to the proportions of subjects who reported an injection site AE.
- **Discontinuations to to AE:** Very few subjects discontinued due to an AE.
- **SAEs:** There were 7 SAEs (1 fatal and 6 nonfatal). None were judged vaccine related by the investigator. One subject in the vaccine group (AN 7494) died of pancreatic cancer during the study (app. 2 years after the third dose of vaccine) but was not included in Table 149 above because this occurred > 15 days after vaccination.
- **AEs following doses 1, 2, and 3:** There were more injection site AEs in the vaccine groups compared to the placebo group, but there were no apparent changes from dose to dose. (Placebo recipients had a somewhat higher AE rate after the first dose as compared to doses 2 and 3, but quadrivalent HPV vaccine recipients did not.) Source: Tables 11-86, 87, 88, p. 637-42, not shown here)
- **AEs and baseline vaccine HPV status:** The proportions of subjects with injection site and systemic AEs was somewhat higher in those who were negative for a vaccine HPV type (either by serology or PCR) as compared to those who were positive by one of tests. However, this pattern was also seen in placebo recipients, so it is difficult to interpret the clinical significance of this finding. (Source: Table 11-89, 11-90, CSR 007, p. 643-6, not shown here)
- **Severity of AEs:** The numbers and percentages of subjects who reported any AE by maximum intensity rating within 15 days after any vaccination were comparable

among the 5 groups. (Source: Table 8-2, CSR 007, p. 301, not shown here) Approximately 92-95% of AEs within 15 days after any vaccination dose were rated as mild to moderate for all treatment groups. The frequency of AEs within each intensity category also appeared comparable among the 5 vaccination groups. (Source: Table 8-3, CSR 007, p. 302, not shown here)

Injection Site AEs in the 5 days after vaccination

- The most common injection site adverse events were pain, erythema, and swelling.
- The incidences of injection site AEs were somewhat higher in the vaccination groups as compared to the placebo group.
- Among the vaccine groups, there was a modest dose response with regard to injection site AEs. (Source: Table 8-4, CSR 007, p. 305-6, not shown here)
- The majority of these events were mild to moderate in severity, although there was a slightly higher percentage of vaccine recipients at the two higher vaccine doses with a severe rating (5.9% and 5.1% for the 40/40/40/40 and 80/80/40/80 doses as compared to 2.9% for the 20/40/40/20 formulation). (Source: Table 8-6, CSR 007, p. 313, not shown here)

Systemic AEs in the 15 days after vaccination

- The most commonly reported systemic AEs were headache and pyrexia. Other more common AEs included abdominal pain, nausea, dysmenorrhea, and throat pain.
- The incidences of systemic AEs were generally comparable among the 5 groups. (Source: Table 8-10, CSR 007, p. 321-7, not shown here)
- The percentages of subjects reporting systemic AEs were somewhat lower after doses 2 and 3 compared to dose 1. (Source: Tables 11-97, 98, 99, CSR 007, p. 658-69, not shown here)

Summary of Temperatures in the 5 days after vaccination

- Per the protocol, any T $\geq$ 100 deg F was to be recorded as a fever.
- The percentages of those with T $\geq$ 38.9 deg F were somewhat higher in the 20/40/40/20 and the 40/40/40/40 mcg formulation as compared to placebo recipients, but were low in all groups (< 2%). (Source: Table 8-14, CSR 007, p. 373, not shown here).

Deaths

- There was one death of a subject 2 years after completing the vaccination phase (AN 7494, 25 yowf, received 20/40/40/20 formulation). This subject died due to pancreatic cancer approximately 2 years following receipt of the third dose of vaccine. The subject's husband informed the study site personnel that the subject was diagnosed with pancreatic cancer in November 2002 (578 days postdose 3), and died on ------- (duration 4.96 months). Hospital records were not available.

Serious Adverse Events

- There were 6 SAEs **within 15 days after vaccination**. There were 4 in the vaccine group and 2 in the placebo group.
  - **Vaccine**
    - **AN 8146**, 24 yowf had **renal colic** 9 days postdose 3 20/40/40/20 vaccine. This subject went on to continue the study.
    - **AN 9258**, 22 yowf had a **worsening of depression** at days 2 postdose 3 20/40/40/20 vaccine. She improved with therapy. The subject was able to continue in the rest of the study.
    - **AN 8285**, 21yoHf had **pyelonephritis** at Day 3 postdose 3 80/80/40/80 vaccine. She was treated and recovered. The subject continued in the study.
    - **AN 7398**, 18 yo wf experienced a **worsening depression** at day 4 postdose 1 of 80/80/40/80 mcg vaccine. The subject was treated, improved, and went on to receive the 2nd and 3rd doses of vaccine without problem.
  - **Placebo:** One subject had severe pyelonephritis 8 days postdose 1 and acute appendicitis day 14 postdose 2.
- The percentages of subjects with SAEs were comparable in the 5 vaccination groups, with small risk differences which were not statistically significant. (Source: Table 8-20, CSR 007, p. 384-5, not shown here)

Subjects who discontinued from the study due to an AE

- **Vaccine**
  - **AN 7149**, 19 yo wf had **swelling at the injection** site 4 inches in diameter postdose 1 40/40/40/40 mcg vaccine, with other AEs including flu, common cold, redness, and pain/tenderness/swelling at the injection site.
  - **AN 7412**, 18 yobf developed **erythema** 2 inches in diameter postdose 2 and pain/tenderness of severe intensity after the 2nd dose of 40/40/40/40 mcg formulation.
- **Placebo:** One subject received 450 mcg alum and discontinued due to numbness in extremities of mild intensity after dose 1. This subject had other AEs (nausea, stomach cramps, sweating palms, and pain/tenderness at the injection site).

Pregnancies

- There were a total of 18 pregnancies: 4 in the placebo group and 14 in the vaccine group. The 2 infants with AEs were twins with respiratory distress (born prematurely). They recovered. Overall pregnancy outcomes are discussed among all trials in the safety summary section.

TABLE 150
Protocol 007: Pregnancy Outcomes by Vaccination Group

Pregnancy Outocme	Placebo N=4	Vaccine Group N=14
Healthy infant	3 (75%)	3 (21.4%)
Elective termination	1 (25%)	4 (28.6%)
Spontaneous abortion	0	2 (14.4%)
Induced abortion	0	1 (7,1%)
Infant AE	0	2 (14.4%)
Unknown	0	3 (21.4%)

Source: Table 8-22, CSR 007, p. 391

New Medical History

- The most common new medical conditions during the vaccination phase were nasopharyngitis, abdominal pain, and vaginal discharge.
- The percentages of subjects who developed these new conditions were comparable among the 5 groups.

Comments-Conclusion Regarding Data for Protocol 007 (Reviewer's Opinion)
Conclusion

- This study demonstrated that there was high vaccine efficacy against persistent HPV infection related to the specific vaccine HPV type(s) in subjects naïve for the relevant vaccine HPV type. There was an indication that the vaccine may also be effective in preventing HPV 6, 11, 16, and 18 related disease, although the number of cases was small, and this could not be ascertained definitively.
- In review of the datasets, there were some subjects who received one of the vaccine formulations and developed CIN. These subjects for the most part appeared to be positive for the relevant vaccine HPV type at Day 1 and developed disease associated with that vaccine HPV type, or developed CIN associated with non-vaccine HPV types.
- The vaccine appeared immunogenic, with peak anti-vaccine HPV GMTs occurring at 1 month following dose 2, and persisting above levels seen with natural infection out to 36 months. An immune correlate of protection has not been identified.
- The vaccine appears to be generally well tolerated. There was no evidence of increased reactogenicity in subjects who were non-naïve for the vaccine HPV types. There was one death due to pancreatic cancer approximately 2 years after receipt of three doses of the 20/40/40/20 mcg formulation. The investigator attribution was that this event was not related to the vaccination.

8.1.4 Trial # 4

Protocol 005: Study of Pilot Manufacturing Lot of HPV 16 Virus Like Particle (VLP) Vaccine in the Prevention of HPV 16 Infection in 16 to 23 year old Women

Study Period: 10/22/98 – 3/31/04

- This study is reviewed here because efficacy results were combined with Protocols 015. 013 and 007 in a combined efficacy report.

Protocol 005 Objectives:

- Demonstration of the safety of the HPV 16 L1 VLP 40 mcg vaccine (administered 0, 2 and 6 months), and the efficacy of the vaccine in preventing persistent HPV 16 infection compared with placebo.
- Secondary objectives included the following:
  - Evaluation of the effect of HPV 16 L1 VLP vaccine on the composite incidence of CIN 1, CIN 2, or CIN 3 due to HPV 16 and on the **composite incidence of CIN 2/3 due to HPV 16**, relative to placebo
  - Evaluation of the relationships among HPV 16 antibody levels, virologic measurements, disease endpoints, and if available, anti-HPV 16 neutralization response; evaluation of the antibody response to HPV 16 L1 VLP vaccine in PCR-positive and seropositive subjects; investigation of the natural history of the development of genital warts.
  - **Please note:** Demonstration that HPV 16 L1 VLP vaccine reduces the viral load of HPV 16 infection compared with placebo **was not assessed.**

Design Overview

- Phase IIa, randomized, multicenter (16), double blind, placebo controlled (alum), efficacy trial

TABLE 151
Protocol 005: Treatment Plan

Treatment Group	N Randomized
HPV 16 L1 VLP Vaccine 40 mcg at 0, 2, and 6 months	1204
Placebo at 0, 2, and 6 months	1205
Total	2409

Source: From Table 6-1, CSR 005, p. 133

TABLE 152
Protocol 005: Vaccine Products Used

Clinical Material	Formulation Number	Dosage	Package
HPV 16 L1 VLP vaccine	V501 HSS009C001	40 mcg/0.5 mL	0.8 mL single-dose vial
HPV 16 L1 VLP vaccine	V501 HSS009C002	40 mcg/0.5 mL	0.8 mL single-dose vial
Placebo	PV501 HSS009A001	Placebo	0.8 mL single-dose vial
Placebo	PV501 HSS009A002	Placebo	0.8 mL single-dose vial

Source: Table 5-4. CSR 005, p. 75

Population: The study was conducted at 16 centers in the U.S. See **APPENDIX 13** for Inclusion/Exclusion criteria, which are similar to the other trials.

Efficacy Endpoints

Primary "efficacy" parameter

- Incidence of persistent HPV 16 infection, including HPV 16 related CIN. A subject was considered to be a case of persistent HPV 16 infection if she was:
  - Seronegative for HPV 16 at Day 0, and HPV 16 DNA negative at Day 0 and Month 7, and fell into one of the following categories: subsequently detected by HPV 16

PCR assay to at least 1 common gene in 2 or more consecutive cervical samples from scheduled visits at least 4 months apart

- Had a cervical biopsy with pathologic evidence of HPV disease as determined by the Pathology Panel [The Pathology Panel included the same pathologists as in Studies 007, 013, and 015; it is noted that Dr. Ronette replaced ---------- in 10/00]
- Demonstrates first time HPV PCR positivity before being lost to follow-up.

Secondary efficacy parameters included

- Detection of HPV 16 on at least one post-Month 7 visit
- HPV 16-related CIN 1, CIN 2, CIN 3, AIS, or cervical cancer
- CIN 1, CIN 2, CIN 3, AIS, or cervical cancer
- The incidence of invasive HPV related procedures (colposcopy with biopsy, definitive therapy, genital warts excision

Exploratory efficacy endpoints (potential therapeutic efficacy) (not all listed):

- The rate of clearance of HPV 16 infection
- The time to clearance of infection
- The rate of progression to clinically apparent HPV 16-related disease

Immunogenicity Endpoints

Primary variable of interest for immunogenicity

- Serum anti-HPV 16 GMTs at Month 7 (4 weeks Postdose 3)

Safety Parameters

- The primary safety parameters were the occurrence of severe injection site reactions and the incidence of any serious vaccine related adverse events.

Protocol 005 Surveillance

TABLE 153
Protocol 005: Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Day 1	Mo 2	Mo 6	Mo 7	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36	Mo 42	Mo 48
Gyn Hx	+			+		+		+		+	+
Gyn PE	+			+		+		+		+	+
Lab:											
Pregnancy test (a)	+	+	+								
Urine GC (PCR or LCR or SDA)	+			+		+		+		+	+
Urine chlamydia (PCR or LCR or SDA)	+			+		+		+		+	+
Lab (b)											
Anti-HPV 16 RIA	+			+	+	+		+		+	+
---------- swabs	+			+							
Swab for HSV culture (if indicated)	+			+		+		+		+	+
Ph Vag fluid (opt)	+			+		+		+		+	+
Wet mount/trich/BV(opt)	+			+		+		+		+	+
Whiff test BV (opt)	+			+		+		+		+	+
KOH for yeast (opt)	+			+		+		+		+	+
---------- swab for HPV PCR	+			+	+	+	+	+	+	+	+
Pap test (Thin Prep) cyto	+			+	+	+	+	+	+	+	+
Colposcopy and cervical biopsy (if indicated) and biopsy thin section PCR											+*
Vaccination (c)	+	+	+								
Clin f/u for safety (d)	+	+	+	+							
Questionnaire (e)	+										+

a. Serum or urine pregnancy test on day of vaccination (urine 25 IU HCG)
b. Serum for Ab may be after gyn exam, before vaccination (MRL)
c. Temp and wt prior to each vaccination
d. Each subject will record on VRC oral temp 4 hours after each injection and daily for the next 4 days. Any injection site or systemic rxn, which occurs on Day 1 or 14 days after each injection, will also be recorded on the VRC. At Months 2, 6, and 7, the study personnel together with the participant reviewed the VRC. At Months 2, 6, and 7, subjects were solicited for any gyn health concerns and any SAEs.
e. All subjects received a self-administered questionnaire at Day 1 and either Month 36 or at early withdrawal.
*A colposcopy, biopsy (if lesion noted colposcopically), and a swab from the biopsy site (if biopsy performed) on all Month 48 subjects.
Source: Table 5-2, CSR 005, p. 67

- All subjects were observed for at least 20 or 30 minutes after each vaccination.
- See Protocol 015 Detailed Safety Cohort for safety follow-up.

Colposcopy Triage Algorithm: See APPENDIX 14.
Reviewer's Comment: The algorithm is similar to Protocol 007 and 013.

Statistical Considerations: See APPENDIX 15 for Changes in Protocol and Changes in Statistical Analyses. Five amendments were submitted to the IND and reviewed prior to unblinding. Changes in statistical analyses did not impact on primary efficacy and safety evaluations.

Primary efficacy hypothesis

- The vaccine was efficacious in preventing persistent HPV 16 infection as compared to placebo, and was tested using a one-sided test of the null hypothesis that vaccine efficacy was 0%. The vaccine would be deemed effective if the lower bound of the 95% CI was > 0%. An exact conditional procedure was used to test this hypothesis. The study employed a fixed number of events design. The power for the primary analysis was determined under the condition that at least 31 cases of sustained PCR 16 positivity were observed. This was expected to occur at app. Month 30. At that point the study would be unblinded, but not to study site staff or lab personnel or subjects. The study was to continue through Month 48, and data collected throughout the rest of the study period were to be used to refine the efficacy estimate of interest and estimate persistence of antibody at the end of the study. The study conclusions regarding vaccine efficacy were to be based primarily on the initial analyses conducted at the time 31 cases have been observed.
- **Time point used for combined efficacy analysis: the sponsor used person years in efficacy point estimates. The timepoints were variable.**

Analysis of safety

- This was based on the assessment of risk differences between vaccine and placebo using the method of Miettenin and Nurminen. Point and 95% CI estimates of risk differences were calculated.

Analysis of immunogenicity

- This was assessed by anti-HPV 16 GMTs and the corresponding 95% confidence intervals at Months 7, 12, 18, 30, 42, and 48.

Handling of dropouts and missing data

Dropouts

- Subjects who had a single HPV 16 DNA detection during the Postdose 3 follow-up period and then subsequently dropped out or lost to follow-up were counted as cases in the primary per-protocol efficacy analysis.

Missing Data

- Subjects who had a definitive therapy procedure without becoming a case of persistent HPV 16 infection were censored for the primary efficacy analysis at the time of the definitive therapy procedure.
- Subjects who had no baseline anti-HPV 16 cRIA result were not eligible to be classified as a case of persistent HPV 16 infection or HPV 16-related disease.

Case Definitions (See Tables 154 and 155 below.)

TABLE 154
Protocol 005

Case Definitions for Subjects Who Have Biopsies Showing Pathologic Evidence of HPV Disease and Who Have Not Had a Loop Electrosurgical Excision Procedure (LEEP) Performed

Sample/Test	Scenario							
	1	2	3	4	5	6	7	8
Cervical sample obtained at visit immediately prior to biopsy—test for HPV 16 by PCR	+	+/–	–	+	+/–	–	–	+
Cervical biopsy—test for HPV 16 by PCR	+	+	+	N/A†	N/A†	N/A†	N/A†	–
Cervical biopsy swab—test for HPV 16 by PCR	N/A†	N/A†	N/A†	+	+	+	–	–
Cervical sample obtained at visit immediately following biopsy—test for HPV 16 by PCR	+/–	+	–	+/–	+	–	–	+
Case Definition	**Case**	**Case**	**Non-case**	**Case‡**	**Case‡**	**Non-case**	**Non-case**	**Case‡**

† N/A = The biopsy swab was only considered in the case definition if biopsy tissue was unavailable for PCR.
‡ Case = This was a case as long as any 2 of the HPV 16 PCR positive samples were at least 4 months apart.
PCR = Polymerase chain reaction assay.
HPV = Human Papillomavirus.

Source: Table 5-6, CSR 005, p. 91

TABLE 155
Protocol 005

Case Definitions for Subjects Who Have Biopsies Showing Pathologic Evidence of HPV Disease and Who Have Had a Loop Electrosurgical Excision Procedure (LEEP) Performed

Sample/Test	Scenario										
	1	2	3	4	5	6	7	8	9	10	11
Cervical sample obtained at visit immediately prior to biopsy—test for HPV 16 by PCR	+	+	+/–	–	–	+	+/–	+	+	+/–	+
Cervical biopsy—test for HPV 16 by PCR	+	+/– or N/A†	+	+	–	N/A†	N/A†	N/A†	+	+	– or N/A†
Cervical biopsy swab—test for HPV 16 by PCR	N/A†	N/A†	N/A†	N/A†	N/A†	+/–	+	+	N/A†	N/A†	N/A†
Cervical biopsy obtained at LEEP—test for HPV 16 by PCR	+/–	+	+	–	+	+	+	–	N/A†	N/A†	N/A†
Cervical biopsy swab obtained at LEEP—test for HPV 16 by PCR	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	+/–	+	+
Case Definition	**Case**	**Case**	**Case**	**Non-Case**	**Non-Case**	**Case**	**Case**	**Case†**	**Case**	**Case**	**Case‡**

† N/A = The biopsy swabs was only considered in the case definition if biopsy tissue was unavailable for PCR. In rare cases, both biopsy tissue and the biopsy swab could have been unavailable (see Scenarios 2 and 11).
‡ Case= This was a case as long as any 2 of the HPV 16 PCR positive samples are at least 4 months apart.
If the only samples available for a subject were the cervical specimens and biopsy swabs (i.e., the subject has no tissue available from any biopsy), the subject was a case only if 2 consecutive specimens taken at least 4 months apart were HPV 16 PCR positive.
PCR = Polymerase chain reaction.
HPV = Human Papillomavirus.

Source: Table 5-7. CSR 005, p. 92

Interim Analysis

- In Protocol 005, an interim analysis was planned at the time when approximately 18 cases of persistent HPV 16 infection or HPV 16 related CIN were accrued.
- The purpose of this interim analysis was to enable administrative decisions to be made regarding future studies.
- The interim analysis was performed by an unblinded Merck statistician unrelated to the HPV program. The unblinded statistician was to perform an analysis of the primary efficacy endpoint at the interim time point using data from the database and a copy of the allocation schedule obtained from a separate source.
- The database and other Merck personnel involved with the HPV program were to remain blinded until the study was complete. The unblinded statistician was to

provide the results of the primary analysis and the conditional power of the study to 5 members of MRL Senior Management representing Research, Clinical, Regulatory and Biostatistics. No Data and Safety Monitoring Board was involved in the interim analysis for this study.

Populations Analyzed

Efficacy Analysis Populations

- The initial efficacy populations were defined differently than those noted in Protocols 007, 013, and 015. However, the definitions were changed to conform with the efficacy analysis populations in the other protocols. (**See Appendix 4.)**

Safety Analysis Population

- All subjects who received at least one injection and had follow-up data were included in the safety summaries for the product actually received.

Immunogenicity Population

- The **per-protocol immunogenicity population** consists of the per-protocol efficacy population further restricted to subjects who (1) received all 3 vaccinations within acceptable day ranges and (2) had serum samples for anti- HPV 16 evaluations collected within the acceptable day ranges.

Changes in protocol and statistical analyses: Five amendments were submitted to the IND and reviewed prior to unblinding. Seeveral changes were made after unblinding, but did not impact on the primary safety and efficacy evaluations. See **APPENDIX 15** for details.

Results

Populations Enrolled/Analyzed

- A total of 2,409 subjects were randomized into the study. Of these randomized subjects, 2391 received at least 1 injection of vaccine or placebo (1193 vaccine recipients and 1198 placebo receipients). (One subject enrolled twice by presenting two sets of identification. She received 5 doses of vaccine, but was counted once in each table).
- A total of 15.1% of the 2,391 subjects discontinued from the study during the vaccination period (Month 0-Month 7). Most subjects who discontinued from the study during this time were either lost to follow-up or withdrew consent. 4 (0.3%) subjects in the vaccine group and 5 (0.4%) in the placebo group discontinued due to an adverse event. 17 (1.4%) of the vaccinees discontinued for “other reasons”, and 9 (0.8%) of the placebo recipients discontinued for “other reasons”. Slightly more vacinees failed to complete this phase as compared to placebo recipients.
- The long term follow-up period was from Month 7 through Month 48 (efficacy follow-up period.) Subjects who completed the vaccination phase were eligible to enter this phase. Among the 2,031 subjects who completed the vaccination phase, 17.7% (360) discontinued study participation during the long term follow period. Most of these subjects were lost to follow-up or withdrew consent. Slightly more placebo recipients failed to complete this phase as compared to vaccinees.

- Overall, 70% of subjects randomized into the study completed both phases of the study.
- 16 sites were involved. One site (Seattle, WA) contributed 20% of subjects; three sites each contributed 10 % of subjects (Iowa City, IA, Indianapolis, IN, and Albuquerque, NM), and the other 50% of subjects were from the 12 remaining sites.

TABLE 156
Protocol 005: Subject Accounting

	HPV 16 L1 VLP Vaccine 40 mcg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Screening Failures					0	
Randomized	1204		1205		2409	
Vaccinated At:						
Dose 1	1193	(99.1)	1198	(99.4)	2391	(99.3)
Dose 2	1092	(90.7)	1120	(92.9)	2212	(91.8)
Dose 3	1019	(84.6)	1053	(87.4)	2072	(86.0)
Dose 4	1	(0.1)	0	(0.0)	1	(0.0)
Dose 5	1	(0.1)	0	(0.0)	1	(0.0)
Vaccination Period (Day 1 To Month 7)						
Entered	1193		1198		2391	
Completed†	993	(83.2)	1038	(86.6)	2031	(84.9)
Discontinued	200	(16.8)	160	(13.4)	360	(15.1)
Clinical AE	4	(0.3)	5	(0.4)	9	(0.4)
Lost to follow-up	88	(7.4)	75	(6.3)	163	(6.8)
Pregnancy	19	(1.6)	14	(1.2)	33	(1.4)
Protocol deviations	22	(1.8)	13	(1.1)	35	(1.5)
Withdrew consent	50	(4.2)	44	(3.7)	94	(3.9)
Other reasons	17	(1.4)	9	(0.8)	26	(1.1)
Long-Term Follow-Up (>Month 7)						
Entered	993		1038		2031	
Completed	835	(84.1)	836	(80.5)	1671	(82.3)
Discontinued	158	(15.9)	202	(19.5)	360	(17.7)
Lost to follow-up	67	(6.7)	69	(6.6)	136	(6.7)
Moved	6	(0.6)	5	(0.5)	11	(0.5)
Pregnancy	0	(0.0)	1	(0.1)	1	(0.0)
Protocol deviations	1	(0.1)	2	(0.2)	3	(0.1)
Withdrew consent	73	(7.4)	104	(10.0)	177	(8.7)
Other reasons	11	(1.1)	21	(2.0)	32	(1.6)

† Subjects completed three doses of vaccinations and entered the long-term follow-up period.
Status percentages were calculated based on the number of subjects who entered the respective time period.
AE = Adverse Experience.
HPV = Human Papillomavirus.
n = Number of subjects in the given category.
VLP = Virus-like Particles.

Source: Table 6-1, CSR 005, p. 133

TABLE 157
Protocol 005: Subject Accounting for the Efficacy and Immunogenicity Analysis Populations by Vaccination Group

	HPV 16 L1 VLP Vaccine 40 mcg (N=1204)	Placebo (N=1205)	Total (N=2409)
Number of Subjects who received at least 1 injection	1193	1198	2391
Per-Protocol Efficacy Population			
Included in Analysis	768	765	1533
Excluded From Analysis	425	433	858
Per-Protocol Immunogenicity Population			
Included in Analysis	684	680	1364
Excluded From Analysis	509	518	1027
Reason for Exclusion from the Analysis Population[†]			
General protocol violation	215	186	401
Incorrectly randomized	3	3	6
Enrolled in another clinical trial	0	1	1
Enrolled more than once	1	0	1
Incorrect clinical material or dose amount	4	8	12
Received non-study vaccination[‡]	15	16	31
Engaged in sexual intercourse within 48 hours of Day 0 or Month 7 visit	2	2	4
Received immunosuppressives, IgG, or blood products	4	12	16
Month 7 swab sample out of acceptable day range	23	13	36
Incomplete vaccination series	174	145	319
Vaccination 2 or 3 out of acceptable day range	88	84	172
Missing Month 7 serology sample/results[§]	27	13	40
Month 7 serum sample out of acceptable day range	59	67	126
Positive to HPV 16[‖]	233	277	510

† Subjects were counted once in each applicable exclusion category. A subject may have appeared in more than one category.
‡ Included live vaccines received within 21 days before or 14 days after study vaccination or inactivated or recombinant vaccines received within 14 days of study vaccination.
§ Among subjects who received all 3 vaccinations.
‖ Seropositive at Day 1 and/or PCR positive to HPV 16 Day 1 through Month 7, inclusive.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
HPV = Human papillomavirus.
MITT = Modified intention-to-treat.
PCR = Polymerase chain reaction.
VLP = Virus like particles.

Source: Table 6-3, CSR 005, p. 136-7

Demographics

- Mean age: 20.1 years.
- Ethnic Distribution: 75% Caucasian, 8.6% blacks, 7.6% Hispanic, 5.9% Asian, 2.0% other, and 1% Native American.
- Smoking Status: 25.4% of subjects were current smokers. (Source: Table 6-5, CSR 005, p. 139, not shown here)

Sexual Demographics

- The median age of sexual debut of subjects in the study overall was 17 years for both the overall study cohort and the PPE cohort. (Source: CSR 005, Table 6-6, p. 142 and Table 11-3, p. 351, not shown here)

Gynecologic History

- Both the overall study cohort and PPE cohort had comparable gynecologic histories.
- 23.2% reported a history of cervicovaginal infection or sexually transmitted disease at study entry in the overall study cohort, and 20.8% of the PPE cohort reported a history of a cervicovaginal infection or sexually transmitted disease at study entry. (Source: CSR 005, Table 6-7, p. 143 and Table 11-4, p. 352, not shown here)

Non-HPV cervicovaginal infections and STDs at Day 1

- Overall, 16.9% of subjects had at least 1 non-HPV cervicovaginal infection.
- The most common were candidal vaginitis, bacterial vaginosis, and Chlamydia cervicitis.
- There were slightly more subjects in the vaccine group with such infections as compared to the placebo group in the overall study cohort (18.2% vaccine vs. 15.6% placebo) and in the PPE cohort (17.7% vs. 12.8% placebo). (Source: CSR 005, Table 6-8, p. 144 and Table 11-5, p. 353, not shown here).

Contraception

- A little more than 50% of vaccinated subjects were using hormonal contraception at entry into the study, and a similar distribution was seen in both the overall study and the PPE cohort. (Source: CSR 005, Table 6-10, p. 146 and Table 11-7, p. 355, not shown here)

HPV Related Pathology at Day 1

- Overall, approximately 17% of subjects had an abnormal Pap test.
- The percentages of subjects in the vaccine and placebo groups with Pap test abnormalities in each cohort were comparable. (Source: CSR 005, Table 6-11, p. 148 and Table 11-8, p. 356, not shown here)

HPV 16 Status at Day 1

- HPV 16 status at Day 1 was evaluated by serostatus (cRIA and ----------) and by HPV DNA PCR status.
- Overall, 18.7% of subjects who were assessed by one of these methods were positive for HPV 16. 14.1% were serostatus positive at Day 1 and 8.6% were positive by PCR. (Source: Table 6-2, CSR 005, p. 151, not shown here)
- The proportions of subjects who were non-naïve for HPV 16 by serology or PCR were similar in the vaccine (17.9%) and placebo (19.4%) groups.

HPV 6, 11, and 18 Detection at Day 1

- 9.2% of subjects were positive for HPV 6, 11, or 18 DNA at Day 1.
- The proportions were comparable between vaccine and placebo recipients. (Source: Table 6-14, CSR 005, p. 154, not shown here)

HPV 6, 11, 16, and 18 Detection at Day 1

- 16.1% of sbjects were positive for HPV 6, 11, 16, or 18 DNA at Day 1.
- 2.1% had two types detected, and 0.1% had three types detected. (Source: Table 6-15, CSR 005, p. 155)

Prior Medication and Vaccination

- Approximately 50% of subjects were using hormonal contraceptives within 3 days prior to the first vaccination.
- Other more common medications were vitamins and anti-inflammatory medications.
- The proportions in the vaccine and placebo groups were comparable. (Source: Table 6-16, CSR 005, p. 157, not shown here)

Concomitant Medication and Vaccinations

- More than 2/3 of subjects reported use of hormonal contraceptives at least once during the 15 days after a vaccination visit.
- The use of medications after vaccination were comparable between the placebo and vaccine groups. (Source: CSR 005, Table 6-17, p. 159-60, not shown here)

Prior Medical History

- The most commonly reported medical condition at enrollment was dysmenorrhea, followed by seasonal allergies and acne.
- With regard to HPV related diagnoses, 3.8% reported a history of genital warts and 3.2% reported a previously abnormal Pap smear.
- Vaccine and placebo groups were comparable in regard to prior medical history. (Source: Table 6-19, CSR 005, p. 163-4, and Table 11-20, CSR 005, p. 390-403, not shown here.)

Measurements of Treatment Compliance

- **Completion of Scheduled Visits During Efficacy Follow-up Period**
  - The vaccine and placebo groups had similar proportions of subjects completing each of the scheduled follow-up visits. (Source: Table 6-20, CSR 005, p. 168, not shown here)
  - Intervals for completing each visit were comparable between the groups as well. (Source: Table 6-21, CSR 005, p. 169, not shown here)

Efficacy Results

Analysis of efficacy was conducted at three time points, and the primary efficacy analysis was in the per-protocol efficacy population (PPE). Other efficacy analyses were conducted in MITT populations.

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Interim Analysis (June 2001)

- This analysis was conducted in preparation of Phase III studies.
- At this analysis, there were zero cases of HPV sustained positivity identified in the vaccine group and 24 cases in the placebo group, and met the statistical criterion for success. The observed efficacy was 100% [95% CI: 83, 100%]. These data were used to proceed into Phase III testing.

Primary (Fixed Case) Analysis (November 2001)

- The protocol specified that the primary efficacy analysis would occur at the time 31 cases of persistent HPV 16 infection occurred in the per protocol population.
- This analysis was conducted by an unblinded statistician not involved in the daily operations of the protocol using data that occurred on or prior to 8/31/01.

- After this analysis, the study remained double blinded (except for the 31 cases of persistent HPV 16 infection) and continued to operate under in house blinding procedures until all remaining subjects completed their protocol specified study visits. These findings were published in November, 2002 (Koutsky et al., NEJM).

Final Analysis (June 2004)

- The study's final analysis was conducted based on the final data set generated after the last subject in the study completed the last protocol specified visit. The last subject visit occurred on 3/31/04.

Primary Analysis: Efficacy Against Persistent HPV 16 Infection

- There were three categories of events:
  - HPV 16 DNA on at least 2 consecutive visits (at least one common gene) conducted at least 4 months apart, without a finding of HPV 16 related CIN.
  - Detection of HPV 16 DNA in a cervical biopsy specimen for the same lesion in which CIN or cervical cancer was detected by the program's Pathology Panel, with detection of HPV 16 DNA immediately prior to or after the CIN or cancer diagnosis.
  - HPV 16 detection on a subject's last study visit without observed persistence.
- Cases of persistent HPV 16 infection were counted starting after Month 7.

TABLE 158
Protocol 005: Analysis of Efficacy Against Persistent HPV 16 Infection
(Per Protocol Efficacy population, Fixed Case Analysis)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Primary Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Persistent HPV 16 infection	753	0	1083.2	0	750	41	1047.2	3.9	**100%**	90.9, 100%
Persistent infectin without HPV 16 related CIN	753	0	1083.2	0	750	31	1047.2	3.0	**100%**	87.8, 100%
Persistent infection with HPV 16 related CIN	753	0	1083.2	0	750	9	1047.2	0.9	**100%**	51.0, 100%
HPV 16 DNA detection before loss to follow-up	753	0	1083.2	0	750	1	1047.2	0.1	**NA**	NA

Source: Table 7-2, CSR 005, p. 175

- At the fixed analysis time point, there were 41 cases of persistent HPV 16 infection in the placebo group and 0 cases in the vaccine group The point estimate of vaccine efficacy was 100% (95% CI:90.9, 100%).

End of Study Final Analysis Of Efficacy
Efficacy Against HPV 16 related persistent infection

- At the final analysis time point, there were 111 cases of persistent HPV 16 infection in the placebo group and 7 cases in the vaccine group.
- 0/7 of vaccine recipients with HPV 16 related persistent infection (detected at the last visit prior to loss to follow-up) had LSIL, HSIL or Pathology Panel CIN at the visit of HPV 16 detection.
- 2/19 of placebo recipients with HPV 16 related persistent infection (detected at the last visit prior to loss to follow-up) had a Pap diagnosis of LSIL at the visit of HPV 16 detection, and 1/19 of these placebo recipients had a Pathology Panel diagnosis of CIN at the visit of HPV 16 detection.
- The point estimate of efficacy in the vaccine group at the end of study was 94.3% (95% CI: 87.8, 97.7%).

TABLE 159
Protocol 005: Analysis of Efficacy Against Persistent HPV 16 Infection
(Per Protocol Efficacy Population, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Primary Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Persistent HPV 16 infection	755	7	2466.8	0.3	750	111	2245.9	4.9	**94.3%**	87.8, 97.7%
Persistent infectin without HPV 16 related CIN	755	0	2466.8	0.0	750	68	2245.9	3.0	**100%**	94.9, 100%
Persistent infection with HPV 16 related CIN	755	0	2466.8	0.0	750	24	2245.9	1.1	**100%**	84.9, 100%
HPV 16 DNA detection before loss to follow-up	755	7	2466.8	0.3	750	19	2245.9	0.8	**NA**	NA

Source: Table 7-3, CSR 005, p. 179

- Twelve subjects were found to have an incident HPV 16 related CIN 2/3 lesions. Among these twelve subjects, only two were found to have had HPV 16 related CIN 1 prior to detection of the HPV 16 related CIN 2/3 lesion. This finding supports previous observations that a multiyear development of CIN 1 phase is not an obligate

prerequisite for the development of CIN 2/3. However, the CIN 1 phase may have been present transiently.

- In 7/12 cases, CIN 2/3 developed after detection of HPV 16 on $\geq$ 2 antecedent visits. This supports previous observations that CIN 2/3 may develop rapidly after acquisition of HPV 16 infection.

Efficacy Against HPV 16 related persistent infection in the MITT populations (fixed cases and final analyses) (See Tables 160 and 161 below).

- In the MITT-3 population, there is a higher point estimate of efficacy at the final analysis (70.6%, 95% CI: 61.2, 78%) as compared to the fixed case analysis time point (59%, 95% CI: 43.3, 70.0%). This may indicate that there is higher efficacy in the population regardless of baseline vaccine HPV status as time progresses. However, please see overall efficacy discussion regarding this issue.

TABLE 160
Protocol 005: Analysis of Efficacy Against Persistent HPV 16 Infection
(MITT Populations, Fixed Case Analysis)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Population	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
MITT-1	784	0	1125.5	0.0	776	42	1078.5	3.9	**100%**	91.2, 100%
MITT-2	824	7	1560.7	0.4	839	76	1516.3	5.0	**91%**	80.7, 96.5%
MITT-3	1004	54	1833.2	2.9	1044	131	1823.6	7.2	**59%**	43.3, 70.0%
MITT-4	969	40	1354.9	3.0	1008	104	1344.1	7.7	**61.8%**	44.6, 74.2%

Source: Table 7-4, CSR 005, p. 186

TABLE 161
Protocol 005: Analysis of Efficacy Against Persistent HPV 16 Infection
(MITT Populations, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Population	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
MITT-1	786	8	2556.1	0.3	777	115	2326.9	4.9	**93.7%**	87.1, 97.3%
MITT-2	824	16	3016.0	0.5	839	150	2779.0	5.4	**90.2%**	83.5, 94.5%
MITT-3	1004	67	3493.2	1.9	1044	217	3325.7	6.5	**70.6%**	61.2, 78%
MITT-4	971	52	3034.2	1.7	1009	192	2878.0	6.7	**74.3%**	64.9, 81.5%

Source: Table 7-5, CSR 005, p. 189

- Table 162 presents the 3 different categories of events that are included in the cases of persistent HPV 16 infection, and point estimates of efficacy at the final analysis at the end of the study.

TABLE 162
Protocol 005: Analysis of Efficacy Against Persistent HPV 16 Infection
(MITT-3 Population, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Primary Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy**	95% CI
Persistent HPV 16 infection	1004	67	3493.2	1.9	1044	217	3325.7	6.5	**70.6%**	61.2, 78.0%
Persistent HPV 16 infection without HPV 16 related CIN	1004	42	3493.2	1.2	1044	139	3325.7	4.2	**71.2%**	59.1, 80.1%
Persistent infection with HPV 16 related CIN	1004	7	3493.2	0.2	1044	43	3325.7	1.3	**84.5%**	65.3, 94.1%
HPV 16 DNA Detected Before Loss to follow-up without HPV 16 related CIN	1004	16	3493.2	0.5	1044	34	3325.7	1.0	**NA**	NA
HPV 16 DNA Detected before loss to follow-up with HPV 16 related CIN	1004	2	3493.2	0.1	1044	1	3325.7	0.0	**NA**	NA

Source: Table 11-28, CSR 005, p. 424

Robustness of Efficacy with Respect to Laboratory Diagnosis

- The source of pathology reading had no impact on the estimate of efficacy. (The vaccine efficacy was still 94.3%, 95% CI: 87.9, 97.8%).

Potential Impact of Missing Data on Estimate of Efficacy

- **Not Imputing Cases Among Subjects Lost to Follow-up:** When vaccine efficacy was re-estimated using cases of HPV 16 identified at the last visit without further follow-up, the vaccine efficacy was 100% (95% CI: 96.3, 100%).
- **Biopsies Outside the Context of the Study:** There were 41 subjects (21 vaccine recipients, 20 placebo) with biopsies done outside of the study. CSR 005 Figures 11-1 and 11-2, p. 426-427, not shown here, provides the outcomes for the subjects who had

biopsies outside the study. In summary, the incidence of biopsies outside the context of the study was low, generally balanced between the vaccine and placebo groups, and had minimal impact on the primary analysis of vaccine efficacy.

Exploratory Analysis of Efficacy with Respect to "Super-Persistent" Infection

- Three definitions of super-persistent HPV 16 infection were used: HPV 16 DNA detected at 3, 4, and 5 consecutive visits. There were no cases of such infections in vaccine recipients. The lower limit of the 95% CI ranged from 69% - 91%, depending on the definition used.

TABLE 163
Protocol 005: Analysis of Efficacy Against "Super-Persistent" HPV 16 Infection
(Per Protocol Efficacy Population, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198					
Endpoint	N	Number of cases	PY at risk	Infection Rate per 100 person years at risk	N	Number of Cases	PY at risk	Infection Rate per 100 person years at risk	**Observed Efficacy**	95% CI
HPV 16 detection at 3 consecutive visits	728	0	2441.2	0	717	41	2277.1	1.8	**100%**	91.2, 100%
HPV 16 detection at 4 consecutive visits	707	0	2405.0	0	697	22	2278.4	1.0	**100%**	82.7, 100%
HPV 16 detection at 5 consecutive visits	682	0	2354.6	0	657	13	2211.0	0.6	**100%**	69.2, 100%

Source: Table 7-13. CSR 005, p. 205

- The proportion of cases of persistent HPV 16 infection in which all grade CIN was detected increased with increasing detection of infection. HPV 16 related CIN was detected among 19% (9/47) of subjects in whom HPV 16 DNA was detected on 2 consecutive visits; 21% (4/19) of subjects in whom HPV 16 DNA was detected on 3 consecutive visits; and 32% (7/22) of subjects in whom HPV 16 DNA was detected on 4 consecutive visits.

Exploratory Analysis of Efficacy With Respect to Clinical Disease: HPV 16 Related CIN, End of Study

- For this analysis, HPV 16 related CIN was defined as detection of HPV 16 DNA on a tissue sample from the same lesion in which CIN was diagnosed by the Pathology Panel, together with detection of HPV 16 DNA on cervicovaginal samples obtained at the post-month 7 visit antecedent to the visit when the biopsy that led to a diagnosis of CIN took place.

- The point estimate of efficacy for all HPV 16 related CIN at the end of study was 100% (See Table 164 below) in the PPE, and VE was similar in the MITT-2 population.

TABLE 164
Protocol 005: Analysis of Efficacy Against HPV 16 Related CIN
(Per Protocol Population, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198				
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy (95% CI)**
HPV 16 related CIN 1 or worse	755	0	2471.9	0	750	24	2379.4	1.0	**100% (84,100%)**
HPV 16 related CIN 2 or worse	755	0	2471.9	0	750	12	2393.9	0.5	**100% (65.1, 100%)**
HPV 16 related CIN 1	755	0	2471.9	0	750	14	2383.8	0.6	**100% (70.9, 100%)**
HPV 16 related CIN 2	755	0	2471.9	0	750	7	2396.0	0.3	**100% (32.7, 100%)**
HPV 16 related CIN 3	755	0	2471.9	0	750	6	2396.2	0.3	**100% (17.7, 100%)**

Source: Table 7-14, CSR 005, p. 207

- In the MITT-3 population, there were 42 cases of HPV 16 related CIN in the placebo group and 7 cases in the vaccine group. The point estimate of efficacy against HPV 16 related 16 CIN 1 or worse was 83.2% (95% CI: 62.2, 93.6%), and the point estimate of efficacy against HPV 16 related CIN 2 or worse was 77.9% (95% CI: 40.6, 93.4%). (See Table 165 below.)

TABLE 165
Protocol 005: Efficacy Against HPV 16 Related CIN
(MITT-3 Population, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198				
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy (95% CI)**
HPV 16 related CIN 1 or worse	1017	7	3683.3	0.2	1050	42	3674.4	1.1	**83.2% (62.2, 93.6%)**
HPV 16 related CIN 2 or worse	1017	5	3640.3	0.1	1050	23	3699.9	0.6	**77.9% (40.6, 93.4%)**
HPV 16 related CIN 1	1017	2	3638.8	0.1	1050	25	3681.8	0.7	**91.9% (67.5, 99.1%)**
HPV 16 related CIN 2	1017	4	3640.4	0.1	1050	13	3703.7	0.4	**68.7% (<0.0, 92.3%)**
HPV 16 related CIN 3	1017	1	3640.6	0.03	1050	11	3704.3	0.3	**90.8% (36.4, 99.8%)**

Source: Table 11-31, CSR 005, p. 429

- There was no change in the number of cases identified when the definition of HPV 16 related CIN included any visit from Month 7 on (instead of the immediate antecedent visit).

Exploratory Analysis of Efficacy With Respect to Clinical Disease: HPV 16 Related Vaginal and Vulvar Lesions

- In the PPE population, there were 3 cases of HPV 16 related vaginal and vulvar lesions in the placebo group, and no cases in the vaccine group. Of these, 2 women had VIN 1, and 1 woman had VaIN 2/3. These numbers were very small, and point estimates of vaccine efficacy were not calculated.

Exploratory Analysis of Efficacy With Respect to Clinical Disease: CIN Due to <u>Any</u> HPV Type.

- For this analysis, a case of CIN is defined as CIN by the Pathology Panel without regard to HPV DNA type, if any, detected on a tissue sample from the lesion examined. There was a positive trend for all CIN grades, although none of the point estimates of efficacy reached statistical significance. (See Table 166 below for PPE population analysis).

TABLE 166
Protocol 005: Efficacy Against CIN Irrespective of HPV Type (Per protocol Efficacy Population with Normal Pap Test Results at Day 1 through Month 7, End of Study)

	HPV 16 40 mcg N=1193				Placebo N=1198				
Endpoint	N	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Observed Efficacy (95% CI)**
CIN 1 or worse	552	34	1801.4	1.9	544	47	1714.7	2.7	**31.1% (<0, 57.1%)**
CIN 2 or worse	552	8	1829.4	0.4	544	16	1748.4	0.9	**52.2% (<0.0, 82.3%)**
CIN 1	552	28	1802.3	1.6	544	38	1719.5	2.2	**29.7% (<0.0, 58.4%)**
CIN 2	552	6	1829.8	0.3	544	10	1751.6	0.6	**42.6% (<0.0, 82.8%)**
CIN 3	552	2	1830.2	0.1	544	7	1751.3	0.4	**72.7% (<0.0, 97.2%)**

Source: Table 7-16, CSR 005, p. 213

- Results of analyses against all CIN irrespective of HPV type in the MITT-2 and MITT-3 were similar to those seen in the PPE population. (Source: Tables 11-32 and 11-33, CSR 005, p. 430-1, not shown here).
  - In the MITT-2 population, the point estimate of efficacy against CIN 2 or worse irrespective of HPV type was 49.1% [95% CI: <0.0, 76.8%].
  - In the MITT-3 population, the point estimate of efficacy against CIN 2 or worse irrespective of HPV type 45.3% [95% CI: 10.9, 67.1%]. It is noted that the point estimate of efficacy against CIN 3 irrespective of HPV type in the MITT-3 population was highest at 70.9% (95% CI: 25.6, 90.4%) at the end of study analysis.

Exploratory Analysis of Eficacy Against Non-Vaccine HPV related Disease

Exploratory Analyses of Efficacy Against Non-Vaccine HPV types, EGLs

- The incidence rates for non-vaccine HPV related EGLs were the same in both the Gardasil and placebo group.
- In this exploratory analysis, there was no evidence of replacement of vaccine HPV types with non-vaccine HPV types in external genital lesions.

TABLE 167
Protocol 005: Incidence of HPV 6, 11, or 18 Related External Genital Lesions (Per Protocol Population within the Relevant HPV Type)

	HPV 16 40 mcg N=1193					Placebo N=1198				
Endpoint	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	95% CI	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	95% CI
HPV 6/11/16/18 related EGLs	904	6	2982.8	**0.2**	(0.1, 0.4)	953	9	3068.2	**0.3**	**(0.1, 0.6)**
HPV 6 EGL	818	3	2710.2	**0.1**	(0.0, 0.3)	865	7	2791.1	**0.3**	**(0.1, 0.5)**
HPV 11 EGL	818	2	2709.7	**0.1**	(0.0, 0.3)	865	2	2796.4	**0.1**	**(0.0, 0.3)**
HPV 18 EGL	869	2	2871.7	**0.1**	(0.0, 0.3)	911	1	2959.9	**0.0**	**(0.0, 0.2)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Table 7-38, CSR 005, p. 265

Exploratory Analysis of Therapeutic Efficacy

Clearance of HPV 16 DNA and Incident HPV 16 related CIN among Subjects who were Seropositive and/or PCR Positive at Baseline

Subjects who were **HPV 16 PCR Positive and Seronegative Subjects at Day 1**: Three analyses were conducted to evaluate the therapeutic efficacy:

- Proportion of subjects who cleared HPV 16 DNA: Little difference between vaccine and placebo groups in the rate of clearance. (Source: Table 7-18, CSR 005, p. 219, not shown here)
- Time to clearance: No apparent difference between vaccine and placebo groups in time to clearance up to app. 2 years since Day 1. (Source: Figure 7-4, CSR 005, p. 220, not shown here)
- Progression to HPV 16 related CIN: The number of cases were small, although the incidence rates were higher in the placebo group as compared to the vaccine group. None of the point estimates of vaccine efficacy reached statistical significance. (Source: Table 7-19, CSR 005, p. 221, not shown here)

- Subjects who were **HPV 16 PCR Positive and Seropositive Subjects at Day 1**: There was no apparent difference between the vaccine and placebo group (in exploratory analyses).
  - Proportion of subjects who cleared HPV 16 DNA: There was a slightly higher clearance rate (42.2% per 100 person-years at risk) in the placebo group as compared to the vaccine group (35.7% per 100 person-years at risk). (Source: Table 7-20, CSR 005, p. 223, not shown here)
  - Time to clearance: No difference between vaccine and placebo groups in time to clearance (although number of subjects is small). (Source: Figure 7-5, CSR 005, p. 224, not shown here)
  - Progression to HPV 16 related CIN 1 or worse: The number of cases was small, and there were a few cases in each group. However, there was one more case of HPV 16 related CIN 1 or worse in the placebo group as compared to the vaccine group. (Source: Table 7-21, CSR 005, p. 225, not shown here)

- Subjects who were **HPV 16 PCR Negative and Seropositive Subjects at Day 1**
  - In an exploratory analysis, the incidence of persistent HPV 16 infection (as assessed by PCR due to reinfection) in the placebo group was 3.8 per 100 person years at risk, and 0.9 per 100 person years in the vaccine group. (Source: Table 7-22, CSR 005, p. 228, not shown here.)

End of Study Pap Tests and Colposcopies- Month 48

- In Study 005 (as in Study 007), colposcopies were performed at the end-of-study Month 48) regardless of the prior Pap test results. There was no apparent vaccine effect on the sensitivity of the Pap test to detect CIN as reported by the sponsor.
- **Pap test Diagnoses:** At the Month 48 visit, a lower proportion of subjects in the vaccine group had Pap test results of LSIL or HSIL compared to placebo recipients. (See Table 168 below).
- **Cervical Biopsy Diagnoses:** At the Month 48 visit, there was a slightly lower proportion of vaccine recipients with CIN 2 or CIN 3 on cervical biopsy compared to placebo recipients. (See Table 169 below).

Table 168
Protocol 005: Month 48 Pap Diagnoses

	Monovalent HPV 16 vaccine N=1193	Placebo N=1198	Total N=2391
Subjects with Pap and colposcopy results at Month 48	827	828	1655
Month 48 Pap diagnosis			
Negative for SIL	695 (84.0%)	684 (82.6%)	1379 (83.3%)
ASC-US HC-II HR Negative	38	42	80
ASC-US HC-II HR Positive	20	17	37
ASC-H	5 (0.6%)	4 (0.5%)	9 (0.5%)
LSIL	60 (7.3%)	68 (8.2%)	128 (7.7%)
HSIL	2 (0.2%)	5 (0.6%)	7 (0.4%)

Source: Table 5.3.5.3.1:1, Statistical Documentation, p. 13

Table 169
Protocol 005: Month 48 Cervical Biopsy Diagnoses

	Monovalent HPV 16 vacine N=1193	Placebo N=1198	Total N=2391
Subjects with Pap and colposcopy results at Month 48	827	828	1655
Subjects with a Month 48 cervical biopsy	217	208	425
Month 48 cervical biopsy diagnosis			
Negative	202 (24.4%)	190 (22.9%)	392 (23.7%)
CIN 1	12 (1.5%)	10 (1.2%)	22 (1.3%)
CIN 2	0 (0.0%)	1 (0.1%)	1 (0.1%)
CIN 3	1 (0.1%)	3 (0.4%)	4 (0.2%)

Source: Table 5.3.5.3.1:5, Statistical Documentation, p. 16

Exploratory Analyses of Immunogenicity

- Table 170 below provides a summary of anti-HPV 16 GMTs by cRIA through Month 48 in the Per Protocol Immunogenicity Population. The analysis of the all HPV 16 naïve with serology population showed similar results with regards to the GMTs. (Source: Table 11-35, CSR 005, p. 434, not shown here)

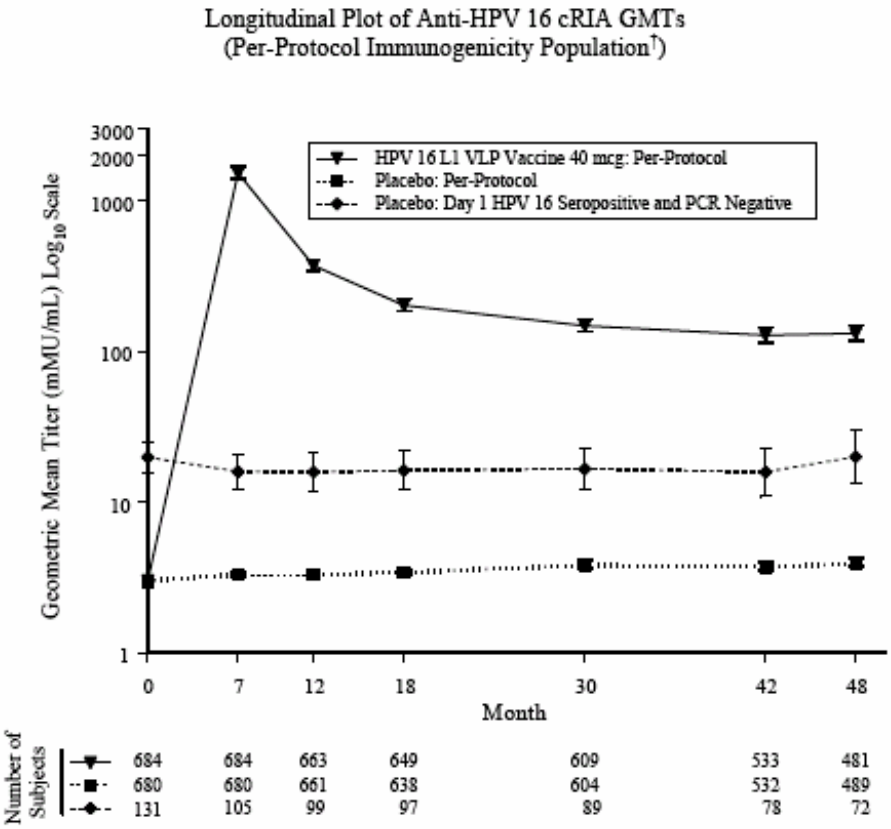
TABLE 170
Protocol 005: Summary of Anti-HPV 16 GMTs by cRIA (PPI Population)

	HPV 16 VLP Vaccine N=1193			Placebo N=1198		
Study Time	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Day 1	684	<6.0	(<6.0, <6.0)	680	<6.0	(<6.0, <6.0)
Month 7	684	1518.8	(1385.5, 1665.0)	680	<6.0	(<6.0, <6.0)
Month 12	663	369.2	(337.0, 404.5)	661	<6.0	(<6.0, <6.0)
Month 18	649	201.8	(184.0, 221.3)	638	<6.0	(<6.0, <6.0)
Month 30	609	147.4	(134.2, 161.8)	604	<6.0	(<6.0, <6.0)
Month 42	533	127.7	(114.1, 143.0)	532	<6.0	(<6.0, <6.0)
Month 48	481	131.5	(116.5, 148.4)	489	<6.0	(<6.0, <6.0)

PPI population for immunogenicity includes subjects who received all 3 vaccinations within acceptable day ranges and had a postvaccination sample collected within acceptable day range.
N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects evaluable at the given study time.
Source: Table 7-23, CSR 005, p. 231

- At Month 7, > 99% (682/684), baseline HPV 16 naïve (i.e., seronegative and PCR negative) subjects who received vaccine were seropositive.
- Figure 26 below provides the longitudinal plot of anti-HPV 16 cRIA GMTs in the PPI population to Month 30. In monovalent HPV 16 vaccine recipients, anti-HPV 16 GMTs remained higher through Month 30 as compared to placebo subjects who were anti-HPV 16 seropositive and HPV 16 PCR negative, or subjects anti-HPV 16 seronegative at baseline.

FIGURE 26
Protocol 005



† Per-protocol population for immunogenicity analysis consisted of the efficacy analysis per-protocol population which received all 3 vaccinations within acceptable day ranges and had a Postvaccination 3 serum sample collected within the acceptable day range.

cRIA = Competitive radioimmunoassay.
GMT = Geometric mean titer.
HPV = Human papillomavirus.
mMu = milli Merck units.
VLP = Virus-like particles.

Source: Figure 7-6, CSR 005, p. 232

Exploratory Analysis of Baseline Factors Possibly Affecting Anti-HPV 16 cRIA Reponses

- The anti-HPV 16 GMTs at Month 7 for minority populations in this U.S. study appeared to be higher in comparison to anti-HPV 16 GMTs for the Caucasian population. (Source: Table 7-26, CSR 005, p. 236-7, not shown here) The clinical significance is uncertain, especially since the assay in this study (cRIA) was different than the assay used in the other efficacy studies.

Impact of Baseline HPV 16 Status on HPV 16 vaccine induced anti-HPV 16 levels

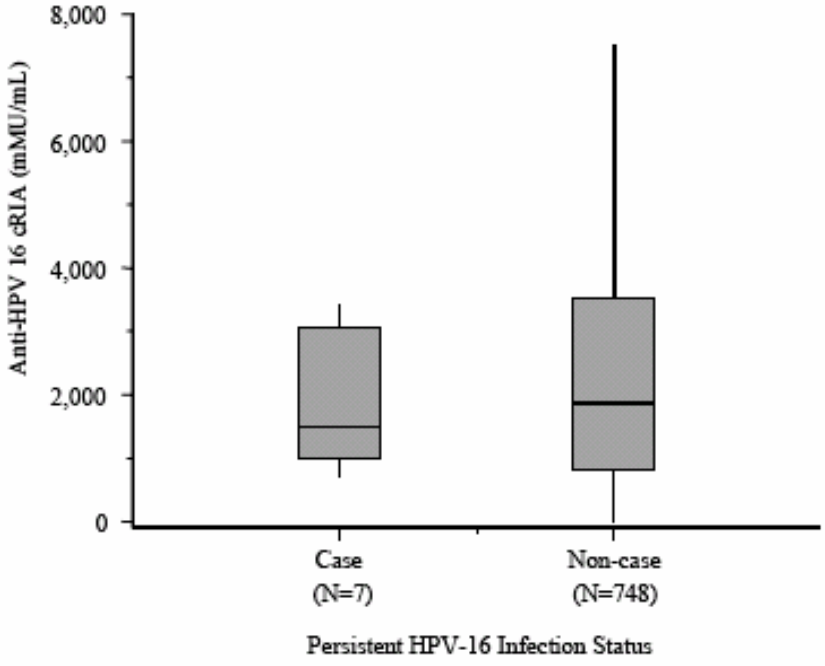
- Baseline seropositivity had a greater impact on increasing the anti-HPV GMT immune response than baseline PCR positivity in vaccine recipients at Months 7 and 48.
  (Source: Table 7-30, CSR 005, p. 248, not shown here)

Exploratory Analysis of Correlates of Protection

- The distribution of the Month 7 anti-HPV 16 cRIA GMTs of the 7 cases among the vaccine recipients did not appear to be different compared with the distribution of the Month 7 anti-HPV 16 cRIA levels of the non-cases. See Figure 27 below.

FIGURE 27

Protocol 005: Distribution of Anti-HPV 16 cRIA Levels at Month 7 in the HPV 16 Vaccine Group (Per Protocol Efficacy Population)



† Efficacy per-protocol population was defined as subjects who generally did not deviate from protocol, received all 3 vaccinations, and were seronegative for HPV 16 at Day 1 and PCR negative for HPV 16 Day 1 through Month 7.
cRIA = Competitive radioimmunoassay.
HPV = Human papillomavirus.
mMu = milli Merck units.
VLP = Virus-like particles.

Source: Figure 7-12, CSR 005, p. 253

Safety outcome

- The proportions of subjects with clinical adverse events were similar for the vaccine and placebo groups.
- There were slightly more injection site adverse events in the vaccine group as compared to the placebo group.
- The proportions of subjects with systemic adverse events were similar for both groups.

- The proportions of subjects who discontinued due to adverse events were comparable in both groups.

TABLE 171
Protocol 005: Clinical Adverse Events Summary
(Days 1 – 15 Following Any Vaccination Visit)

	HPV 16 L1 VLP Vaccine N=1191	Placebo N=1196
Subjects with follow-up	1126	1149
Subjects with 1+ AE	1048 (93.1%)	1053 (91.6%)
Subjects with 1+ IS AE	974 (86.5%)	945 (82.2%)
Subjects with 1+ systemic AE	803 (71.3%)	825 (71.8%)
Subjects with SAEs	4 (0.4%)	3 (0.3%)
Subjects who died	0 (0.0%)	0 (0.0%)
Subjects who discontinued due to AE	4 (0.4%)	5 (0.4%)

N=number of subjects who actually received the vaccine material corresponding to the indicated vaccination group.
n=number of subjects belonging to the category being reported
Source: Table 8-1, CSR 005, p. 275

Intensity of AEs

- In the 15 days after vaccination, the majority of adverse events were rated as mild to moderate in both vaccine and placebo groups, and the rates of both the percentage of subjects who reported any adverse event and the frequency of intensity ratings of all adverse events reported were similar. (Source: Tables 8-2 and 8-3, CSR 005, p. 276-7, not shown here)

AEs after doses 1, 2, 3

- The overall incidences of clinical adverse events were comparable among both groups after dose 1, 2, and 3.
- There was a somewhat higher percentage of subjects reporting an adverse event in both groups after dose 1 (83.3% vaccine, 82.8% placebo) as compared to dose 2 (73.8% vaccine, 69.7% placebo) and dose 3 (74.9% vaccine, 68.4% placebo). (Source: Tables 11-36, 11-37, 11-38, CSR 005, p. 435-7, not shown here)

Impact on baseline serostatus and HPV 16 DNA status on overall clinical adverse events

- The overall incidences of adverse events were comparable for vaccine recipients in the following groups based on baseline HPV 16 status: seronegative and HPV 16 DNA negative; seronegative and HPV 16 DNA positive; seropositive and HPV 16 DNA negative; and seropositive and HPV 16 DNA positive. (Source: Tables 11-39, 11-40, 11-41, and 11-42, CSR 005, p. 438-41, not shown here)

Injection Site AEs (Days 1-5)

There was a higher proportion of subjects with an injection site reaction in vaccine recipients as compared to placebo recipients. There was a statistically higher incidence of injection site pain, swelling, and erythema in the vaccine recipients as compared with placebo recipients. (See Table 172 below)

TABLE 172
Protocol 005: Injection Site Adverse Events within 5 days of injection

Comparison of Vaccination Groups With Respect to Number (%) of Subjects Who Reported Specific Injection-Site Adverse Experiences With ≥1% Incidence in One or More Vaccination Groups (Days 1 to 5 Following Any Vaccination Visit)

	HPV 16 L1 VLP Vaccine 40 mcg (N= 1191)		Placebo (N= 1196)		Risk Difference (HPV 16 L1 VLP Vaccine - Placebo)	95% CI	p-Value†
	n	(%)	n	(%)			
Subjects with no follow-up	65		47				
Subjects with follow-up	1126		1149				
Number (%) of subjects with one or more injection-site adverse experiences	974	(86.5)	945	(82.2)	4.3	(1.3, 7.3)	
Injection Site Bruising	69	(6.1)	61	(5.3)	0.8	(-1.1, 2.8)	
Injection Site Erythema	335	(29.8)	286	(24.9)	4.9	(1.2, 8.5)	0.009†
Injection Site Pain	950	(84.4)	924	(80.4)	4.0	(0.8, 7.1)	0.013†
Injection Site Pruritus	33	(2.9)	21	(1.8)	1.1	(-0.2, 2.4)	
Injection Site Reaction	2	(0.2)	11	(1.0)	-0.8	(-1.6, -0.2)	
Injection Site Swelling	288	(25.6)	211	(18.4)	7.2	(3.8, 10.6)	<0.001†

† Statistically significant at 0.05 level, unadjusted for multiple comparisons. Unadjusted p-values significant at the 0.05 level were provided only for adverse experiences prompted on the vaccination report card.
Percentages were based on the number of subjects with follow-up after any vaccination visit.
N = The number of subjects who actually received the vaccine material corresponding to the indicated vaccination group. There was one subject randomized to the HPV 16 L1 VLP vaccine group who received placebo and then discontinued study participation. There was 1 subject randomized to the placebo group who received one vaccination of HPV 16 L1 VLP vaccine and then discontinued study participation. These 2 subjects were included in the counts reported in this table. There were 2 subjects randomized to the HPV 16 L1 VLP vaccine group and 2 subjects randomized to the placebo group and who received mixed vaccine material. These 4 subjects were not included in the counts reported in this table. Therefore, this table reports N=1191 (1193 minus 2) subjects vaccinated with HPV 16 L1 VLP vaccine and N=1196 (1198 minus 2) subjects vaccinated with placebo.
n = Number of subjects who reported injection site adverse experience 1 to 5 days following any vaccination visit.
HPV = Human papillomavirus.
VLP = Virus-like particles.

Source: Table 8-5, CSR 005, p. 281

Intensity of Injection Site AEs within 5 days of vaccination

- The incidences of subjects rating the injection site adverse events as severe were comparable between the vaccine and placebo groups.
- The proportion of subjects who reported their most intense adverse injection site adverse event as moderate was higher in the vaccine group (26.5%) as compared to the placebo group (19.5%) (Source: Table 8-6, CSR 005, p. 282, not shown here)
- When the incidences of injection site adverse events are compared among those who are sero-, DNA-; sero-, DNA+; sero+, DNA-; and sero+, DNA+, there are comparable results among the vaccine groups, and generally comparable results between the vaccine and placebo groups. (Source: Tables 11-53, 11-54, 11-55, 11-56, CSR 005, p. 452-5, not shown here)

Systemic Adverse Events within 15 days of vaccination

- The vaccine and placebo groups were generally comparable with respect to the proportion of subjects who reported any systemic adverse events within 15 days of vaccination, and the risk differences for specific adverse events were small. (Source: Tables 8-10 and 8-11, CSR 005, p. 288-95, not shown here)
- The incidences of specific systemic AEs in the vaccine and placebo groups were similar. (Source: Table 11-57 CSR 005, p. 456-65, not shown here).

Intensity of Systemic AEs within 15 days of vaccination

- The two groups were generally comparable with respect to the proportion of subjects whose most intense systemic adverse event was classified as moderate (35.1% vaccine, 36.4% placebo) or severe (16.8% vaccine, 16.3% placebo). (Source: Table 8-12, CSR 005, p. 296, not shown here)
- In addition, the two groups were generally comparable with respect to the proportion of systemic adverse events classified by subjects as moderate (42.2% vaccine, 44.3%% placebo) or severe (10.6% vaccine, 11.6% placebo) in intensity. (Source: Table 8-13, CSR 005, p. 297, not shown here)
- When the incidences of systemic adverse events are compared among those who are seronegative, DNA-; sero-, DNA+; sero+, DNA-; and sero+, DNA+, there are comparable results among the vaccine groups, and generally comparable results between the vaccine and placebo groups. (Source: Tables 11-61, 11-62, 11-63, 11-64, CSR 005, p. 472-82, not shown here)

Temperatures within 5 days after vaccinations

- The incidences of increased temperatures (2.5% vaccinees - 3.6% placebo recipients) were quite low in both groups, and comparable. (Source: Table 8-14, CSR 005, p. 299, not shown here)
- There was no statistical difference between the incidence of maximum oral Temperature $\geq$ 37.8 deg C ($\geq$ 100 deg F) in the vaccine and placebo groups. (Source: Table 8-15, CSR 005, p. 300, not shown here)

Deaths: There were two deaths throughout the entire study period, one in each group.

- **AN 01009:** A 25 year old white female who received the vaccine, and was killed in a plane crash 3 years after the 3rd dose of vaccine.
- **AN 01092:** A 21 year old white female who received placebo, and committed suicide 2 years after the 3rd dose of placebo.

Reviewer's Comment: These do not appear related to administration of study material.

Nonfatal serious adverse events: There were 37 such events (18 vaccine, 19 placebo).
SAEs in Vaccine Recipients included the following:

- **OB-GYN SAEs:** Ruptured ovarian cyst 83 days following dose 2, (hospitalized), recovered, then lost to follow-up; ectopic pregnancy resulting in fetal death 81 days following dose 2, outpatient surgery, recovered, received 3rd dose; bilateral ovarian cysts 34 days following dose 3, (hospitalized for surgery), recovered; torn perineum 272 days following dose 1 at time of delivery of healthy infant, hospitalized, recovered; blood clot near placenta 128 days after dose 3 (85 days after the first positive pregnancy test) and was hospitalized, fetal death (> 20 weeks) occurred 85 days after the first positive pregnancy test; dysfunctional uterine bleeding 2 days postdose 1, had D&C 11 days after start of bleeding, diagnosed with hemorrhage, negative pregnancy, hormonal disorder, recovered. (Latter assessed as probably not related by investigator).
- **Cardiac SAEs:** Hemorrhage after cardiac ablation 135 days following dose 2, diagnosis WPW, hospitalized overnight, recovered; syncope 5 days following dose 1; subject with history of left ventricular disease since birth, hospitalized, and had repeat

syncopal episode during the hospitalization (reportedly like previous episodes prior to vaccination), recovered, continued in study.

- **GI SAEs:** Nausea, vomiting, dehydration 38 days following dose 1 (subject with history of SLE), hospitalized, recovered, continued; gall bladder attack 63 days following dose 1 (hospitalized), recovered.
- **GU SAEs: p**yelonephritis 7 days following dose 2, (hospitalized), recovered, continued.
- **Respiratory SAEs:** Asthma exacerbation 88 days following dose 2 (hospitalized), recovered, continued; asthma attack 56 days following dose 2, (hospitalized), recovered. (Assessed as probably not related by investigator.)
- **Other SAEs:** 2 Orthopedic events and 3 Psychiatric events**.**

SAEs in Placebo Recipients included the following:

- **OB-GYN**: included ruptured ovarian cyst 27 days following dose 3
- **Cardiac disorders**: Pneumonia, pericarditis, and anemia 8 days following dose 2.
- **GI event:** appendicitis 23 days following dose 2.
- **GU Events**: 2 subjects with pyelonephritis (42 days following dose 1 and and 54 days following dose 1)
- **Respiratory event:** asthma exacerbation 109 days following dose 2 [probably not related as per investigator].
- **Other SAEs:** 7 Orthopedic/injury events and 5 Psych events

Discontinuations due to AE: 4 vaccine, 5 placebo. All recovered.

- **Vaccine discontinuations:** rash after dose 1 associated with stomach ache, erythema at site, pain at site which was probably related to vaccine; asthma exacerbation following dose 1 which was probably related; headache, nausea and somnolence following dose 1; multiple AEs following dose 2 [back pain, headache, meningismus, nausea, neck pain, pyrexia, dehydration, dizziness, paresthesia, and vomiting].
- **Placebo discontinuations**: hives following dose 1; hives following dose 2; feeling ill following dose 2; eczema following dose 2; facial rash following dose 1.

Risk differences for SAEs and severe injection site AEs

- Fewer than 2% of each group had a SAE (each with 1.7%), and did not reach statistical significance. (Source: Table 8-20, CSR 005, p. 315, not shown here).
- 2.3 and 2.5% of placebo and vaccine recipients, respectively, had a severe injection site AE and the risk difference did not reach statistical significance. (Source: Table 8-21, CSR 005, p. 316, not shown here)

Medical History during Vaccination Period

- The proportions who reported one or more medical conditions were comparable between the vaccine and placebo groups.
- The 3 most common medical conditions during this time in vaccinees were abnormal Pap test, URI, and vaginal discharge.
- The 3 most common medical conditions during this time in placebo recipients were URI, abnormal Pap test, and UTI. (Source: Table 8-22, CSR 005, p. 318-9, not shown here)

Medical History during the Efficacy Follow-Up Period

- The two groups had comparable proportions of subjects who reported one or more new medical conditions.
- The rates of immune system disorders, non-HPV gynecologic infections, and rash were also comparable between the two groups. (Source: Table 8-23, CSR 005, p. 320-2, not shown here)

Pregnancy Outcomes:

- There were 68 subjects, distributed evenly between the 2 vaccination groups, who reported a total of 69 pregnancies that occurred from Day 1 through Month 7.

TABLE 173
Protocol 005: Outcomes of Pregnancies that Occurred from Day 1 through Month 7 by Vaccination group

	HPV 16 40 mcg Vaccine N=1191	**Placebo N=1196**
	N (%)	N (%)
Subjects who became pregnant	34 (2.9%)	34 (2.8%)
Pregnancy Outcomes		
Full term without complications	15 (44.1%)	6 (17.6%)
Full term with complications to mother	2 (5.9%)	1 (2.9%)
Spontaneous abortion/miscarriage	6 (17.6%)	5 (14.7%)
Elective Abortion	7 (20.6%)	18 (52.9%)
Unknown	4 (11.8%)	4 (11.8%)

Source: Table 8-24, CSR 005, p. 323

- The spontaneous abortions occurred at various times postvaccination.
- There was a higher proportion of placebo recipients who had an elective abortions.

Comments-Conclusion Regarding Data for Protocol 005 (Reviewer's Opinion)

- This Phase IIa protocol demonstrated efficacy of the monovalent HPV 16 vaccine (40 mcg) against persistent HPV 16 infection. The vaccine appeared immunogenic in a very high proportion of individuals. There was no apparent safety signal identified, and there was no indication of excessive AEs in those who were non-naïve to HPV 16.
- There was evidence of efficacy against both HPV 16 related CIN 2/3 and against any HPV related CIN 2/3 in the MITT-3 population.

Other Trials
Trial #5: Use of Gardasil in young adolescents
Protocol 016: A Study to Demonstrate Immunogenicity and Tolerability of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents, and to Determine End-Expiry Specifications for the Vaccine
Study Period: 12/7/02 – 9/20/04
Frozen file achieved on 11/2/04, and the database was unblinded on 11/19/04.

Objectives:
Primary Safety Objectives:
- To demonstrate that a 3-dose regimen of quadrivalent HPV VLP vaccine is generally well tolerated in adolescents and young adults.

Immunogenicity Objective for Adolescent Substudy:
- To demonstrate that quadrivalent HPV vaccine, when given in a 3-dose regimen, results in similar anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 in girls 10 to 15 years of age and in boys 10 to 15 years of age as in women 16 to 23 years of age.

Immunogenicity Objective for Expiry Dose Substudy:
- To identify the minimum partial dose formulation of quadrivalent HPV vaccine among the 20, 40, or 60% partial dose formulations, given in a 3-dose regimen, that will induce similar immune responses to administration of a 3-dose regimen of full dose quadrivalent HPV vaccine, for each HPV type contained in the vaccine.

Design:
- Protocol 016 was composed of 2 substudies: the Adolescent Immunogenicity substudy and the End-Expiry substudy.
  - **Adolescent Immunogenicity Substudy** was a multicenter immunogenicity and tolerability study conducted in 3 groups: 16- to 23-year-old females, 10- to 15-year-old females, and 10- to 15-year-old males. All subjects were to receive a 3-dose regimen of quadrivalent HPV vaccine 20/40/40/20 mcg.
  - **End-Expiry Substudy**, a multicenter expiry dose and tolerability study conducted in groups: 16- to 23-year-old female subjects and 10- to 15-year-old female subjects. Subjects from both groups were randomized to receive a 3-dose regimen of 20, 40, 60, or 100% dose formulation of the quadrivalent HPV vaccine 20/40/40/20 mcg.

TABLE 174
Protocol 016: Dose Arms

Group	Group Name	Quadrivalent HPV Vaccine				Number Enrolled			
		HPV 6 L1 VLP (mcg)	HPV 11 L1 VLP (mcg)	HPV 16 L1 VLP (mcg)	HPV 18 L1 VLP (mcg)	16- to 23-Year-Old Females	10- to 15-Year-Old Females	10- to 15-Year-Old Males	Total
I	100% Phase III Dose Formulation	20	40	40	20	500	500	500	1500
II	60% Phase III Dose Formulation	12	24	24	12	250	250	---	500
III	40% Phase III Dose Formulation	8	16	16	8	250	250	---	500
IV	20% Phase III Dose Formulation	4	8	8	4	250	250	---	500
	Total	--	--	--	--	1250	1250	500	3000

Source: Table 1-1, p. 52. CSR -16v1

- Of the 3000 subjects planned for enrollment in Protocol 016, 1250 were to be 16- to 23-year-old females, 1250 were to be 10- to 15-year-old females, and 500 were to be 10- to 15-year-old males.
- The female cohorts were randomized in a 1:1:1:2 ratio to receive 20, 40, 60, or 100% dose quadrivalent vaccine.
- All of the males received full-dose vaccine. All subjects in Group I (see Table 174 above) participated in the Adolescent Immunogenicity Substudy.
- All female subjects participated in the End-Expiry Substudy.

Vaccine Products Used

TABLE 175
Protocol 016: Adolescent Immunogenicity Substudy
Vaccine Products Used

Product	Lot Number	Dosage	Route of Administration
Quadrivalent HPV L1 VLP vaccine (100%)	V501VAI020I004	20/40/40/20 mcg + 225 mcg aluminum adjuvant/0.5 mL	IM injection

TABLE 176
Protocol 016: End Expiry Substudy
Vaccine Products Used

Product	Lot Number	Dosage	Route of Administration
Quadrivalent HPV L1 VLP vaccine (100%)	V501VAI020I004	20/40/40/20 mcg + 225 mcg aluminum adjuvant/0.5 mL	IM injection
Quadrivalent HPV L1 VLP vaccine (60%)	V501VAI022Q001	12/24/24/12/mcg + 225 mcg aluminum adjuvant/0.5 mL	IM injection
Quadrivalent HPV L1 VLP vaccine (40%)	V501VAI023R001	8/16/16/8 mcg + 225 mcg aluminum adjuvant/0.5 mL	IM injection
Quadrivalent HPV L1 VLP vaccine (29%)	V501VAI024S001	4/8/8/4 mcg + 225 mcg aluminum adjuvant/0.5 mL	IM injection

Population:

- **Protocol 016** was conducted in 61 centers worldwide in 19 countries in 4 geographic areas. The countries included Australia, Brazil, Canada, Colombia, Costa Rica, France, Germany, Greece, Guatemala, Israel, Netherlands, Philippines, Portugal, Spain, Sweden, Taiwan, Thailand, United Kingdom, and the United States.

Inclusion Criteria: 10-15 Year Old Males

- Healthy males age 10 to 15 years.
- Must not yet have had coitarche and did not plan on becoming sexually active through the course of the study.
- No temperature $\geq$ 100°F or $\geq$ 37.8°C (oral) within 24 hours prior to the first injection.

Inclusion Criteria: 10-15 Year Old Females

- In addition to above, not pregnant at the time of enrollment.

Inclusion Criteria: 16-23 Year Old Females

- Same as in Protocols 013 and 015 (see **APPENDIX 1**)

Exclusion Criteria: All subjects

- Same as for Protocols -13 and 015 (see **APPENDIX 1**)

Exclusion Criteria: 16- 23 Year Old Females

- Individuals with any prior abnormal Pap test with SIL or ASC-US, ASC-H, or diagnosis of CIN.
- Individuals with prior history of genital warts or treatment for genital warts.
- Individuals with > 4 lifetime male or female sexual partners.

Vaccination Schedule

- Subjects received vaccine formulations or placebo (0.5 mL) IM at 0, 2, and 6 months.

Endpoints

Primary Immunogenicity Endpoints

- Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs at Month 7
- Proportion of subjects who were HPV 6, 11, 16, or 18 naïve at baseline and became seropositive to the relevant HPV type 4 weeks Postdose 3.

Primary Safety Endpoints:

- Occurrence of severe injection site AEs
- The incidence of any vaccine related SAEs

TABLE 177
Protocol 016: Study Flow Chart: 10-15 Year Old Males and Females

Event/Test	Consent Visit (Day 1)	Visit 2 Month 2	Visit 3 Month 3	Visit 4 Month 6	Visit 5 Month 7	Visit 6 Month 12
Information brochure/prescreening	X					
Informed consent	X					
Medical History/PE	X					
Pregnancy Test	X	X		X	X	
Serum for antibody measurements						
Anti-HPV 6, 11, 16, 18 cLIA	X		X		X	
Retention serum, stored frozen at site	X		X		X	
Vaccination	X	X		X		
Clinical follow-up for safety	X	X	X	X	X	X

Source: Table 5-1, CSR 016v1, p. 63

Additional Procedure for Young Adolescent Population

- If a subject in the 10- to 15- year-old group was found to have an anti-HPV cLIA level above the negative assay cutoff at Day 1, the result was to have been communicated to the primary investigator who enrolled that subject. The investigator was then required to communicate the finding to the subject and the subject's parent/guardian, together with appropriate counseling regarding the meaning of this finding (i.e., that the subject may have engaged in consensual or non-consensual sexual activity), as well as what follow-up may be necessary. (Due to laws in effect in Sweden, Day 1 serology results for subjects enrolled in that country were not reported to the investigator or to the subjects or the subjects' parents/guardians.) A high degree of certainty that a positive HPV assay result represented a true finding (rather than a false positive) was needed for parental/guardian notification of a positive HPV result. Therefore, the sponsor set up a second, higher cutoff to reduce false positive results.
- For older women, educational materials were provided regarding HPV infection and disease.

TABLE 178
Protocol 016: Study Flow Chart: 16-23 Year Old Females

Event/Test	Consent Visit Day 1	Visit 2 Month 2	Visit 3 Month 3	Visit 4 Month 6	Visit 5 Month 7
Consent	+				
Gyn Hx	+				+
Gyn PE	+				+
Medical history/Physical Examination	+				
Pregnancy test	+	+		+	+
Urine GC (PCR or LCR or SDA) (optional)	+				+
Urine chlamydia (PCR or LCR or SDA) (optional)	+				+
Anti-HPV (6,11,16,18) cLIA	+		+		+
Retention serum, stored frozen at study site	+		+		+
HPV assay standard development (optional)					+
---------- swabs	+				+
Swab for HSV culture (optional	+				+
Ph Vag fluid (optional)	+				+
Wet mount/trich/BV(optional)	+				+
Whiff test BV (optional)	+				+
KOH for yeast (optional)	+				+
---------- swab	+				+
Pap test (Thin Prep) cytology	+				+
Vaccination	+	+		+	
Clin f/u for safety	+	+	+	+	+

Source: Table 5-2, CSR -16v1, p. 67

Safety Follow-up:

- These are as noted in Protocol 013.
- At the Month 12 visit for the 10-15 year old subjects, which consisted of a telephone interview, the parents of the 10-15 year old subjects were solicited for any new medical conditions that may have occurred.
- Participants had also been instructed to notify the study physician in the event of any unexpected or severe AE.

Statistical Considerations for Immunogenicity

- **Adolescent Immunogenicity Substudy**
  - The **primary immunogenicity objective of the substudy** was to demonstrate that the quadrivalent HPV vaccine, when given in a 3-dose regimen, results in noninferior anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 in 10- to 15-year-old females and in 10- to 15-year-old males, as compared to 16- to 23-year-old females. Two co-primary hypotheses were tested to address this objective, and both had to be met to declare that immune responses were similar:
    - The quadrivalent HPV vaccine induces non-inferior immune responses, as measured by the **GMTs** to HPV 6, 11, 16, and 18 at Week 4 Postdose 3, in 10- to 15-year-old females or 10- to 15-year-old males, as compared to 16- to 23-year-old females. The sponsor's statistical criterion for non-inferiority requires

that the lower bound of the 95% CI on the fold-difference in GMTs between the two groups excludes a decrease of 2-fold or more for each of the HPV types.
    - The quadrivalent HPV vaccine induces noninferior immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in 10- to 15-year-old females or 10- to 15-year-old males, as compared to 16- to 23- year-old females. Seroconversion was defined as changing serostatus from seronegative to seropositive. Seropositive was defined as anti-HPV serum cLIA levels ≥20, 16, 20, 24 milli-Merck Units/mL for HPV types 6, 11, 16, and 18, respectively.
    - The sponsor's statistical criterion for non-inferiority requires that the lower bound of the 95% CI on the difference in proportions between the 2 groups excludes a decrease of 5 percentage points or more for each HPV type. The 10-15 year old males were compared to the 16-23 year old women, and the 10-15 year old girls were compared with the 16-23 year old women.
- **End-Expiry Substudy**
  - At least one partial dose formulation of the quadrivalent HPV vaccine given in a 3-dose regimen induces similar immune responses to those elicited by the full dose formulation of the quadrivalent HPV vaccine, with respect to each of the vaccine HPV types (6, 11, 16, 18), as measured by GMTs at week 4 posdose 3.
  - Each HPV type will be analyzed separately.
    - The statistical criterion for similarity requires that the LB of the multiplicity-adjusted 95% CI for the fold-difference in GMTs between the two groups (partial dose/full dose) exclude a decrease of 2-fold or more for each vaccine HPV type. Success requires similarity for all 4 vaccine HPV types.

Immunogenicity Analysis Populations

- **Per-Protocol Population for Immunogenicity** analysis included all **s**ubjects without protocol violations who received all 3 vaccinations within acceptable day ranges, who were seronegative at Day 1 and (16- to 23-year-old females only) PCR negative Day 1 through Month 7 to the respective HPV type(s), and who had a valid serology result within an acceptable day range following the third injection.
- **All Type-Specific HPV-Naïve Subjects With Serology Data Population**: The all type-specific HPV-naïve subjects with serology data population included all subjects who were seronegative at Day 1 and (16- to 23-year-old females only) PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a valid Month 7 serology result within acceptable day range. This population included general protocol violators and considered incorrectly randomized subjects in the analysis according to the vaccination group to which they were randomized.

Changes in Protocol and Statistical Analysis: Three amendments were submitted to the IND and reviewed prior to unblinding. The only change in the planned statistical analysis after unblinding was the age range for the study, which was written in the Data Analysis Plan as 9 to 15 years of age, but the true age range for the study [as specified in the protocol] was 10 to 15 years of age. See **APPENDIX 16 for** details**.**

Results
Protocol 016-Adolescent Immunogenicity Substudy: Population Enrolled/Analyzed

TABLE 179
Protocol 016-Adolescent Immunogenicity Substudy:
Population Enrolled/Analyzed And Subject Disposition

	10-15 year old females	10-15 year old males	16-23 year old females	Total
	n/%	n/%	n/%	n/%
Subjects screened but not enrolled (failure to meet I/E criteria)				55
Randomized	506	510	513	1529
Vaccinated at:				
Dose 1	506 (100%)	508 (99.6%)	511 (99.6%)	1525 (99.7%)
Dose 2	499 (98.6%)	495 (97.1%)	495 (96.5%)	1489 (97.4%)
Dose 3	494 (97.6%)	489 (95.1%)	467 (91.0%)	1450 (94.8%)
Completed Vaccination and Completed Study	482 (95.3%)	483 (95.1%)	465 (91.0%)	1430 (93.8%)
Completed study at Month 7	242 (47.8%)	278 (54.7%)	465 (91.0%)	985 (64.6%)
Completed study at Month 12	240 (47.4%)	205 (40.4%)	0 (0.0%)	445 (29.2%)
Discontinued Vaccination but continued study	0 (0.0%)	2 (0.4%)	8(1.6%)	10 (0.7%)
Completed study at Month 7	0 (0.0%)	1 (0.2%)	8 (1.6%)	9 (0.6%)
D/C vax due to Clinical AE	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
D/C vax due to pregnancy	0 (0.0%)	0 (0.0%)	7 (1.4%)’	7 (0.5%)
Completed study at Month 12	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
D/C vax due to other reasons	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Discontinued from study	24 (4.7%)	23 (4.5%)	38 (7.4%)	85 (5.6%)
At or before Month 7	15 (3.0%)	20 (3.9%)	38 (7.4%)	73 (4.8%)
Clinical AE	1 (0.2%)	2 (0.4%)	0 (0.0%)	3 (0.2%)
Lost to f/u	7 (1.4%)	9 (1.8%)	20 (3.9%)	36 (2.4%)
Moved	0 (0.0%)	0 (0.0%)	2 (0.4%)	2 (0.1%)
Other reasons	0 (0.0%)	0 (0.0%)	2 (0.4%)	2 (0.1%)
Parent withdrew consent	1 (0.2%)	4 (0.8%)	0 (0.0%)	5 (0.3%)
Withdrew consent	6 (1.2%)	5 (1.0%)	14 (2.7%)	25 (1.6%)
After Month 7	9 (1.8%)	3 (0.6%)	0 (0.0%)	12 (0.8%)
Lost to f/u	9 (1.8%)	3 (0.6%)	0 (0.0%)	12 (0.8%)

Source: Table 6-1, CSR 016v1, p. 111-12

- The sponsor notes that the percentage of subjects completing Month 12 was 44% because some of the subjects had completed the study at Month 7 before the protocol amendment extending follow-up to Month 12 was approved at their sites.

Protocol 016-End Expiry substudy: Population Enrolled/Analyzed

TABLE 180
Protocol 016-End Expiry Substudy: Subject Disposition

	20%	40%	60%	100%	Total
	n/%	n/%	n/%	n/%	n/%
Subjects screened but not enrolled (failure to meet I/E criteria)					49
Randomized	504	514	508	1019	2545
Vaccinated at:					
Dose 1	503 (99.8%)	513 (99.8%)	508 (100.0%)	1017 (99.8%)	2541 (99.8%)
Dose 2	493 (97.8%)	504 (98.1%)	490 (96.5%)	994 (97.5%)	2481 (97.5%)
Dose 3	473 (93.8%)	495 (96.3%)	478 (94.1%)	961 (94.3%)	2407 (94.6%)
Completed Vaccination and Completed Study	465 (92.4%)	489 (95.3%)	471 (92.7%)	947 (93.1%)	2372 (93.3%)
Completed study at Month 7	353 (70.2%)	367 (71.5%)	346 (68.1%)	707 (69.5%)	1773 (69.8%)
Completed study at Month 12	112 (22.3%)	122 (23.8%)	125 (24.6%)	240 (23.6%)	599 (23.6%)
Discontinued Vaccination but completed study	1 (0.2%)	2 (0.4%)	6 (1.2%)	8 (0.8%)	17 (0.7%)
Completed study at Month 7	1 (0.2%)	2 (0.4%)	5 (1.0%)	8 (0.8%)	16 (0.6%)
D/C vax due to Clinical AE	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)
D/C vax due to pregnancy	0 (0.0%)	2 (0.4%)	5 (1.0%)	7 (0.7%)	14 (0.6%)
Completed study at Month 12	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.0%)
D/C vax due to other reasons	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.0%)
Discontinued from study	37 (7.4%)	22 (4.3%)	31 (6.1%)	62 (6.1%)	152 (6.0%)
At or before Month 7	34 (6.8%)	19 (3.7%)	28 (5.5%)	53 (5.2%)	134 (5.3%)
Clinical AE	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)
Lost to f/u	16 (3.2%)	6 (1.2%)	11 (2.2%)	27 (2.7%)	60 (2.4%)
Moved	3 (0.6%)	1 (0.2%)	2 (0.4%)	2 (0.2%)	8 (0.3%)
Other reasons	1 (0.2%)	1 (0.2%)	0 (0.0%)	2 (0.2%)	4 (0.2%)
Parent withdrew consent	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.1%)	4 (0.2%)
Pregnancy	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Protocol deviation	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Withdrew consent	9 (1.8%)	10 (1.9%)	14 (2.8%)	20 (2.0%)	53 (2.1%)
After Month 7	3 (0.6%)	3 (0.6%)	3 (0.6%)	9 (0.9%)	18 (0.7%)
Lost to f/u	1 (0.2%)	3 (0.6%)	3 (0.6%)	9 (0.9%)	16 (0.6%)
Withdrew consent	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)

Source: Table 6-1, CSR 016v2, p. 105-6

Reasons for exclusion in the adolescent immunogenicity study

- Among 10-15 year old adolescents, the most common reasons for exclusion from the PPI population were collections of Month 7 serology sample outside the specified day range, and failure to complete the 3-dose vaccination regimen.
- Among 16-23 year old women, the most common reasons for exclusion from the PPI population were baseline positivity to vaccine HPV types, collection of blood outside prespecified day ranges, and failure to complete 3-dose vaccination.

TABLE 181
Protocol 016 – Adolescent Immunogenicity Substudy:
Summary of Subjects Excluded from the PPI Populations by Group

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (100% Formulation)			Total
	10- to 15-Year-Old Females (N=506)	10- to 15-Year-Old Males (N=510)	16- to 23-Year-Old Females (N=513)	(N=1529)
	n	n	n	n
Subjects who received at least 1 injection	506	508	511	1525
Subjects excluded from Per-Protocol Population				
HPV 6/11	80	77	191	348
HPV 16	79	78	205	362
HPV 18	77	76	171	324
Subjects included in Per-Protocol Population				
HPV 6/11	426	431	320	1177
HPV 16	427	430	306	1163
HPV 18	429	432	340	1201
Reason for exclusion:				
General protocol violation	34	33	66	133
Vaccine storage temperature out of range	2	1	0	3
Incorrectly randomized	1	0	0	1
Enrolled more than once	0	0	1	1
Incomplete vaccination series	12	19	44	75
Incorrect dose or incorrect clinical material	1	0	2	3
Received non-study vaccination[†]	12	8	11	31
Received immunosuppressives, IgG, or blood products	4	6	10	20
Engaged in sexual intercourse (applies to 10- to 15-year-olds only)	3	0	N/A	3
Day 1 serum or swab[‡] sample or results missing	0	0	14	14
Month 7 serum sample or results missing[§]	4	4	4	12
Month 7 serum sample out of acceptable day range[§]	21	15	50	86
Month 7 swab sample or results missing[‡,§]	N/A	N/A	19	19
Positive to HPV 6 or 11[‖]	10	5	51	66
Positive to HPV 16[‖]	7	5	64	76
Positive to HPV 18[‖]	6	2	27	35

Source: Table 6-2, CSR 016v1, p. 115

Reasons for Exclusion in the End Expiry Substudy

- The most common reasons for exclusion from the PPI population were baseline positivity for one or more vaccine HPV type, Month 7 serum sample collected outside of acceptable day range, and incomplete vaccination regimen.

TABLE 182
Protocol 016-End Expiry Substudy:
Summary of Subjects Excluded from the PPI population

	20% N=504	40% N=514	60% N=508	100% N=1019	Total N=2545
	n	n	n	n	n
Subjects who received at least 1 injection	503	513	508	1017	2541
Subjects excluded from PPI population					
HPV 6/11	128	120	138	271	657
HPV 16	135	136	138	284	693
HPV 18	118	105	124	248	595
Subjects included in PPI population					
HPV 6/11	375	393	370	746	1884
HPV 16	368	377	370	733	1848
HPV 18	385	408	384	769	1946
Reasons for exclusion					
General protocol violations	72	60	78	141	351
Vaccine storage out of T range	3	1	0	2	6
Incorrectly randomized	0	0	0	1	1
Enrolled more than once	0	0	0	1	1
Incomplete vaccination series	30	18	30	56	134
Vaccination 2 or 3 out of day range	33	27	33	49	142
Incorrect dose or material	0	0	1	3	4
Received non-study vaccine	3	5	8	23	39
Received immunosuppressives, IgG, or blood	7	9	9	14	39
Engaged in sexual intercourse (10-15 year olds)	1	2	3	3	9
Day 1 serum or swab results missing (latter-16-23 yo)	0	0	0	12	12
Month 7 serum sample missing	6	4	4	8	22
Month 7 serum out of day range	32	36	30	71	169
Month 7 swab missing (16-23 year old)	0	0	0	19	19
Positive for HPV 6 or 11	28	28	31	61	148
Positive for HPV 16	41	42	32	71	186
Positive for HPV 18	15	9	12	33	69

Source: Table 6-2, CSR 016v2, p. 109-110

Demographic and Baseline Characteristics

- The 61 sites were located in 4 geographic regions: North America (US and Canada), Europe (France, Germany, Greece, Israel, Netherlands, Portugal, Spain, Sweden, United Kingdom), Latin America (Brazil, Colombia, Costa Rica, Guatemala) and Asia (Australia, Philippines, Taiwan, Thailand).

TABLE 183
Protocol 016 -Adolescent Immunogenicity Substudy: Subjects Enrolled by Region

Region	**10-15 year old females N=506**	**10-15 year old males N=510**	**16-23 year old females N=513**	**Total N=1529**
Asia-Pacific	95 (18.8%)	147 (28.8%)	112 (21.8%)	354 (23.2%)
Europe	89 (17.6%)	61 (12.0%)	153 (29.8%)	303 (19.8%)
Latin America	154 (30.4%)	80 (15.7%)	85 (16.6%)	319 (20.9%)
North America	168 (33.2%)	222 (43.5%)	163 (31.8%)	553 (36,2%)

Source: From Table 6-4, CSR 016v1, p. 118-9

- The baseline characteristics of the PPI population in the adolescent immunogenicity substudy were similar to the overall study cohort. (Source: Table 11-3, CSR 016v1, p. 238, not shown here)

TABLE 184
Protocol 016 – Adolescent Immunogenicity Substudy: Summary of Subject Characteristics by Demographic Cohort

	10-15 year old females N=506	10-15 year old males N=510	16-23 year old females N=513	Total N=1529
Age (years)				
Mean	12.6 years	12.6 years	20.0	15.1
Range	10-15	10-15	16-23	10-23
Weight (kg)				
Mean	50.8	53.1	60.6	54.9
Range	23-141	24-129	32-126	23-141
BMI				
Mean	20.8	20.8	23.0	21.6
Range	12-51	12-38	14-51	12-51
Race				
Asian	59 (11.7%)	86 (16.9%)	59 (11.5%)	204 (13.3%)
Black	30 (5.9%)	23 (4.5%)	33 (6.4%)	86 (5.6%)
Hispanic American	85 (16.8%)	49 (9.6%)	58 (11.3%)	192 (12.6%)
Native American	0 (0.0%)	5 (1.0%)	0 (0.0%)	5 (0.3%)
White	321 (63.4%)	341 (66.9%)	354 (69.0%)	1016 (66.4%)
Other	11 (2.2%)	6 (1.2%)	9 (1.8%)	26 (1.7%)
Smoking Status				
Never smoked	N/A	N/A	349 (68.0%)	349 (68.0%)
Current smoker			118 (23.0%)	118 (23.0%)
Ex-smoker			45 (8.8%)	45 (8.8%)

Source: Table 6-4, CSR 016v1, p. 118-119

- The proportions of subjects enrolled per region were comparable among the treatment groups in the end-expiry substudy. The baseline characteristics of the PPI population in the end expiry substudy were similar to the overall study cohort. (Source: Table 11-2, CSR 016v2, p. 211, not shown here)

TABLE 185
Protocol 016 -End Expiry Substudy: Subjects Enrolled by Region

Region	**20% Formulation N=504**	**40% Formulation N=514**	**60% Formulation N=508**	**100% Formulation N=1019**	**Total N=2545**
Asia-Pacific	101 (20%)	102 (19.8%)	101 (19.9%)	207 (20.3%)	511 (20.1%)
Europe	121 (24.0%)	124 (24.1%)	122 (24.0%)	242 (23.7%)	609 (23.9%)
Latin America	120 (23.8%)	120 (23.3%)	120 (23.6%)	239 (23.5%)	599 (23.5%)
North America	162 (32.1%)	168 (32.7%)	165 (32.5%)	331 (32.5%)	826 (32.5%)

Source: From Table 6-4, CSR 016v2, p. 116

- The baseline characteristics of the PPI population in the end expiry substudy were similar to the overall study cohort shown in Table 186 below. (Source: Table 11-2, CSR 016v2, p. 211, not shown here)

TABLE 186
Protocol 016 – End Expiry Substudy:
Summary of Subject Characteristics by Demographic Cohort-

	20% Formulation N=504	40% Formulation N=514	60% Formulation N=508	100% Formulation N=1019	Total N=2545
Age (years)					
Mean	16.2 years	16.5 years	16.2 years	16.3 years	16.3 years
Range	10-23 years	10-24 years	10-23 years	10-23 years	10-24 years
Race					
Asian	56 (11.1%)	58 (11.3%)	57 (11.2%)	118 (11.6%)	289 (11.4%)
Black	36 (7.1%)	33 (6.4%)	30(5.9%)	63 (6.2%)	162 (6.4%)
Hispanic American	74 (14.7%)	74 (14.4%)	74 (14.6%)	143 (14.0%)	365 (14.3%)
White	334 (66.3%)	339 (66.0%)	340 (66.9%)	675 (66.2%)	1688 (66.3%)
Other	4 (0.8%)	10 (1.9%)	7 (1.4%)	20 (2.0%)	41 (1.6%)
Smoking Status					
Never smoked	164 (65.1%)	162 (62.5%)	162 (63.3%)	349 (68.0%)	837 (65.4%)
Ex- smoker	25 (9.9%)	20 (7.7%)	24 (9.4%)	45 (8.8%)	114 (8.9%)
Current smoker	63 (25.0%)	77 (29.7%)	70 (27.3%)	118 (23.0%)	328 (25.6%)

Source: Table 6-4, CSR 016v2, p. 116

Sexual Demographics for 16-23 year old women

- App. 10% of these subjects had a history of CV infection at study entry. (Source: Table 6-6, CSR 016v1, p. 122, not shown here)
- App. 19.5% had a previous pregnancy. (Source: Table 6-7, CSR 016v1, p. 123, not shown here)
- Most of these subjects (app. 69%) used hormonal contraception, and 38% used barrier methods. (Source: Table 6-8, CSR 016v1, p. 124, not shown here)
- Of subjects with a satisfactory Pap smear, 8.1% had a Pap test suggestive of SIL at enrollment, with the most common abnormalities being ASC-US and LSIL (3.8% each). (Source: Table 6-9, CSR 016v1, p. 125)

Anti-HPV Serostatus and HPV PCR Status at Day 1-Adolescent Immunogenicity Substudy

HPV Serostatus

- Very few of the 10-15 year old females or males were seropositive to one of the vaccine HPV types.

TABLE 187
Protocol 016: Summary of HPV Serostatus at Day 1 by Demographic Cohort

	Gardasil 100% formulation					
HPV Type	**10-15 year old females N**	**n/% Positive**	**10-15 year old males N**	**n/% Positive**	**16-23 year old females N**	**n/% Positive**
Anti-HPV 6, 11, 16, or 18	506	19 (3.8%)	508	7 (1.4%)	511	70 (13.7%)
Anti-HPV 6	506	9 (1.8%)	508	5 (1.0%)	511	32 (6.3%)
Anti-HPV 11	506	2 (0.4%)	508	2 (0.4%)	511	6 (1.2%)
Anti-HPV 16	506	7 (1.4%)	508	5 (1.0%)	511	37 (7.2%)
Anti-HPV 18	506	6 (1.2%)	508	2 (0.4%)	511	11 (2.2%)

Source: Table 6-10, CSR 016v1, p. 127

HPV 6, 11, 16, 18 Detection at Day 1

- This was only conducted for 16-23 year old women. In a composite analysis, 19.4% of these women were seropositive and/or PCR positive for a vaccine HPV type. (Source: Table 6-13, CSR 016v1, p. 130, not shown here)

Anti-HPV Serostatus and HPV PCR Status at Day 1-End Expiry Substudy

- For each vaccine HPV type, a majority of subjects within each group was naïve at baseline (90%-92%). (The groups each included 10-15 year old girls, assessed by serology, and 16-23 year old women, assessed by serology and HPV PCR.) (Source: Table 6-5, CSR 016v2, p. 118, not shown here)
- In a composite analysis, 2.5% of the 10-15 year old subjects were positive at Day 1 to one of the vaccine HPV types by serology. (Source: Table 6-9, CSR 016v2, p. 125, not shown here)

- In a composite analysis, 21.0% of the 16-23 year old subjects were non-naive to one of the vaccine HPV types by PCR and/or serology. (Source: Table 6-8, CSR 016v2, p. 124, not shown here)

The treatment groups in each substudy were comparable for concomitant medications and vaccinations, prior medications, prior medical history, and treatment compliance.

Immunogenicity Results-Adolescent Immunogenicity Substudy

- **GMTs:** As noted in Table 188 below, the 10-15 year old males had the highest numerical GMT values at Month 7 (4 weeks postdose 3), and 10-15 year old females with the next highest GMTs. The 16-23 year old women had the lowest GMT values of the 3 groups. The younger age groups also had higher GMTs numerically at Month 3.

TABLE 188
Protocol 016 - Adolescent Immunogenicity Substudy:
Summary of anti-HPV cLIA GMTs by Group
(PPI Population) at Month 7

Assay	10-15 year old females N=506		10-15 year old males N=508		16-23 year old females N=511	
	n	GMT 95% CI	n	GMT 95% CU	n	GMT 95% CI
Anti-HPV 6	426	989.8 (907.7, 1079.2)	431	1118.6 (1025.5, 1220.3)	320	603.0 (548.5, 662.9)
Anti-HPV 11	426	1270.6 (1159.5, 1392.3)	431	1399.6 (1274.9, 1536.6)	320	739.2 (665.5, 821.0)
Anti-HPV 16	427	4873.0 (4374.1, 5428.9)	430	5962.1 (5362.7, 6628.5)	306	2753.0 (2400, 3157.3)
Anti-HPV 18	429	957.7 (861.3, 1064.8)	432	1241.6 (1113.8, 1384.1)	340	470.5 (418.5, 528.9)

Source: Table 7-1, CSR 016v1, p. 148

- **Seroconversion:** Almost all of the subjects in the PPI cohort seroconverted by Month 3 (4 weeks postdose 2).

TABLE 189
Protocol 016 - Adolescent Immunogenicity Substudy: Summary of the Proportions of Subjects who Became Seropositive to Vaccine HPV type by Group (PPI Population) at Month 3 and Month 7

Assay	10-15 year old females N=506		10-15 year old males N=508		16-23 year old females N=511	
	n	% Seroconversion 95% CI	n	% Seroconversion 95% CI	n	% Seroconversion 95% CI
Anti-HPV 6						
Month 3	417	100% (99.1, 100%)	430	100% (99.1, 100%)	315	100% (98.8, 100%)
Month 7	426	100% (99.1, 100%)	431	100% (99.1, 100%)	320	100% (98.9, 100%)
Anti-HPV 11						
Month 3	418	100% (99.1, 100%)	430	100% (99.1, 100%)	315	100% (98.8, 100%)
Month 7	426	100% (99.1, 100%)	431	100% (99.1, 100%)	320	100% (98.9, 100%)
Anti-HPV 16						
Month 3	419	99.8% (98.7, 100%)	429	100% (99.1, 100%)	302	100% (98.8, 100%)
Month 7	427	100% (99.1, 100%)	430	100% (99.1, 100%)	306	100% (98.8, 100%)
Anti-HPV 18						
Month 3	421	98.8% (97.3, 99.6%)	431	98.6% (97.0, 99.5%)	334	97.6% (95.3, 99.0%)
Month 7	429	100% (99.1, 100%)	432	99.8% (98.7, 100%)	340	99.1% (97.4, 99.8%)

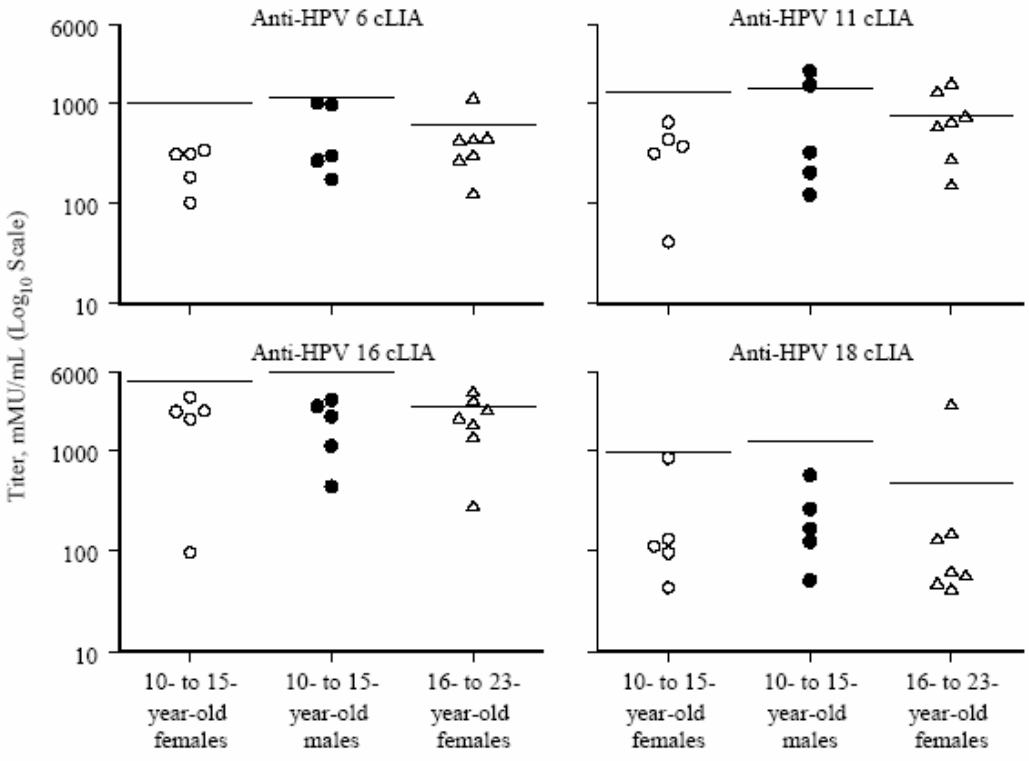
Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for HPV 6, 11, 16, and 18 cLIAs for the purpose of primary immunogenicity analysis were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Table 7-2, CSR 016v1, p. 149

- 21 subjects failed to become seropositive to at least 1 vaccine HPV type at Month 3 and/or Month 7.
  - Of these, 20/27 subjects failed to become anti-HPV 18 seropositive and 1 subject failed to become anti- HPV 16 and anti-HPV 18 seropositive.
  - The proportion of the 21 subjects who did not become seropositive in the 16-23 year old age group was higher (47.6%) compared to the younger age group (33.6%).
  - These 16-23 year old subjects who did not seroconvert to at least 1 HPV type at Month 3 and/or Month 7 were heavier than the overall 16-23 year old cohort (mean weight 77.5 kg vs. 60.6 kg). (Source: Table 11-14, CSR 016v1, p. 283, not shown here)
  - 17 subjects failed to become anti-HPV 16 and/or anti-HPV 18 seropositive at Month 3, but did become seropositive to both types at Month 7. The sponsor reported that these subjects responded less vigorously to each of the 4 components of the quadrivalent vaccine as compared to those in the PPI population. In these 17 subjects, 94% (16/17) of Month 7 anti-HPV 6 levels were below the Month 7 anti-HPV 6 GMT for the relevant demographic group; 76% (13/17) of Month 7 anti-HPV 11 levels were below the Month 7 anti-HPV 11 GMT for the relevant demographic group; 88% (15/17) of Month 7 anti-HPV 16 levels were below the

Month 7 anti-HPV 16 GMT for the relevant demongraphic group; and 94% (16/17) of Month 7 anti-HPV 18 levels were below the Month 7 anti-HPV 18 GMT for the relevant demongraphic group. This is shown in Figure 28 below.

FIGURE 28
Protocol 016

Month 7 Titers in 17 Subjects in the PPI† Population Who Failed to Become Anti-HPV 16
and/or Anti-HPV 18 Seropositive at Month 3 but Became Seropositive to Both Types at Month 7 Compared to PPI Population GMTs



——— GMT in the respective demographic group

† The PPI population included all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and (16- to 23-year-old females only) PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; PPI = Per-protocol immunogenicity.

Source: Figure 11-1, CSR 016v1, p. 287

- **Comparison of GMTs and Seroconversion Rates**
  - To test the primary immunogenicity hypothesis, the immune responses among 10- to 15-year-old females were compared to the immune responses among 16- to 23-year-old females, and the immune responses among 10- to 15-year-old males were compared to the immune responses among 16- to 23-year-old females. These

comparisons were performed for both GMTs and the proportions of subjects who seroconverted based on the anti-HPV cLIAs.

- Observationally, the 16- to 23-year-old females have lower GMTs than the 10- to 15-year-olds at each time point for all regions. The interaction was considered quantitative in nature, and both primary comparisons of GMTs (10- to 15-year-old females vs. 16- to 23- year-old females) were performed based on all regions, with a model that adjusted for geographic region, demographic group, and demographic-group-by-geographic-region interaction.
- Table 190 below displays the s**tatistical analysis of non-inferiority of Month 7 HPV cLIA GMTs in the PPI population.** For each HPV type, the statistical criterion for success required that the lower confidence bound exceed 0.5. Because the lower bound exceeded 0.5 for all HPV types, the criterion was met, supporting the conclusion that GMTs in 10- to 15-year-old females are noninferior to those in 16- to 23-year-old females.

TABLE 190
Protocol 016: Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA GMTs Comparing 10-15 Year Old Females to 16-23 Year Old Females (PPI Population)

	Comparison Group					
	10-15 year old females Comparison group A N=506		16-23 year old females Comparison Group B N=511			
Assay	N	**Estimated GMT (mmU/mL)**	N	**Estimated GMT (mmU/mL)**	Estimated Fold Difference Group A/Group B (95% CI)	p-value for non-inferiority
Anti-HPV 6	426	**960.0**	320	**574.9**	**1.67** (1.46, 1.91)	< 0.001
Anti-HPV 11	426	**1224.8**	320	**705.9**	**1.74** (1.50, 2.00)	< 0.001
Anti-HPV 16	427	**4713.3**	306	**2548.0**	**1.85 (**1.55, 2.21)	< 0.001
Anti-HPV 18	429	**918.4**	340	**452.9**	**2.03** (1.72, 2.39)	< 0.001

Source: Table 7-3, CSR 016v1, p. 161

- Table 191 below displays the **statistical analysis of non-inferiority comparing** 10- to 15- year-old females to 16- to 23-year-old females with regard to the proportion who became **seropositive** to each vaccine HPV type by Month 7 in the PPI population. Because the lower bound exceeded -5.0 percentage points for all HPV types, the criterion was met, supporting the conclusion that the proportions of 10- to 15-year-old females who became seropositive to vaccine HPV types were non-inferior to those observed in 16- to 23-year-old females.

TABLE 191
Protocol 016: Statistical Analysis of the Non-Inferiority with Comparing Month 7 Seroconversion Rates in 10-15 Year Old Females with 16-23 Year Old Females (PPI population)

Assay	Comparison Group: 10-15 year old females Comparison Group A N=508		Comparison Group: 16-23 year old females Comparison Group B N=511		Estimated Percentage Point Difference Group A-Group B (95% CI)	p-value for non-inferiority
	N	**Estimated Response (%)**	N	**Estimated Response (%)**		
Anti-HPV 6 ≥ 20 mMU/mL	426	**100%**	320	**100%**	**0.0** (-0.9, 1.3)	< 0.001
Anti-HPV 11 ≥ 16 mMU/mL	426	**100%**	320	**100%**	**0.0** (-0.9, 1.3)	< 0.001
Anti-HPV 16 ≥ 20 mMU/mL	427	**100%**	306	**100%**	**0.0** (-0.9, 1.3)	< 0.001
Anti-HPV 18 ≥ 24 mMU/mL	429	**100%**	340	**99.2%**	**0.8** (-0.2, 2.5)	<0.001

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for the HPV 6, 11, 16, and 18 cLIAs were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Table 7-5, CSR 016v1, p. 163

- Each of the comparisons was conducted for the all HPV naïve with serology population, and the results are similar. (Source: Tables 11-22, -23, -24, -25, CSR 016v1, p. 295-8, not shown here)
- The statistical comparisons for immune responses for 10-15 year old males and 16-23 year old females (by GMTs and percentages who seroconverted) also demonstrated non-inferiority of immune responses in 10-15 year old males compared to 16-23 year old females. (Source: Table 7-4, CSR 016v1, p. 162 and Table 7-6, CSR 016v1, p. 164).

Exploratory Immunogenicity Summary

- **Immunogenicity Response among anti-HPV seropositive subjects at Day 1**
  - When compared observationally with the anti-HPV GMTs induced among the PPI population, the GMTs in these Day 1 seropositive subjects were higher at both the Month 3 and Month 7 visits. (Source: Tables 7-7 and -8, CSR 016v1, p. 167-8, not shown here).
- **Immunogenicity Response among HPV PCR Negative and anti-HPV Seropositive in 16-23 year old women**
  - When compared observationally with the anti-HPV GMTs induced among the PPI population of 16- to 23-year-old females, the anti-HPV GMTs in these anti-HPV seropositive at baseline vaccinees were higher at both the Month 3 and Month 7 visits. (Source: Tables 7-11, 7-12, CSR 016v1, p. 171-2, not shown here)

- **Immunogenicity Response among HPV PCR Positive and anti-HPV Seropositive in 16-23 year old women**
  - The GMTs in these baseline HPV PCR-positive and anti-HPV seropositive populations were higher at both the Month 3 and Month 7 visits. However, the sample sizes were very small for each of the HPV types. (Source: Tables 7-13, 7-14, CSR 016v1, p. 173-4, not shown here)

Immunogencity Evaluation: End Expiry Substudy

- Within each vaccination group, GMTs for each vaccine HPV type increased from Day 1 to 30 days postdose 2 (Month 3) and from Postdose 2 to 30 days postdose 3 (Month 7). In general, there was a general dose response for anti-HPV 6, 11, 16, 18 GMT with increasing dose formulations at 4 weeks postdose 2 (Month 3) and 4 weeks postdose 3 (Month 7).

TABLE 192
Protocol 016- End Expiry Substudy: Summary of HPV cLIA GMTs by Vaccination Group (PPI Population)

		20% formulation N=503		**40% formulation N=513**		**60% formulation N=508**		**100% formulation N=1017**	
Assay	Time point	n	GMT 95% CI	n	GMT 95% CI	n	GMT 95% CI	n	GMT 95% CI
Anti-HPV 6	**Month 3**	372	349.7 (320.1, 382.0)	384	413.5 (378.2, 452.1)	359	511.6 (461.5, 567.1)	732	541.2 (508.5, 575.9)
	Month 7	375	**585.5** (528.4, 649.3)	393	**704.2** (636.6, 779.0)	370	**711.9** (637.4, 795.1)	746	**800.2** (748.9, 855.0)
Anti-HPV 11	**Month 3**	372	360.4 (328.8, 395.1)	384	461.6 (420.0, 507.3)	359	557.0 (500.0, 620.4)	733	671.7 (627.3, 719.3)
	Month 7	375	**635.3** (568.3, 710.2)	393	**805.4** (724.9, 894.8)	370	**843.5** (751.1, 947.4)	746	**1007.2** (937.7, 1081.7)
Anti-HPV 16	**Month 3**	365	1434.6 (1261.9, 1630.8	368	1770.1 (1551.9, 2019.0)	358	1914.7 (1648.9, 2223.4)	721	2294.9 (2093.2, 2516.0)
	Month 7	368	**2411.4** (2094.3, 2776.5)	377	**2962.6** (2594.4, 3383.0)	370	**3136.9** (2724.3, 3612.1)	733	**3839.5** (3518.7, 4189.6)
Anti-HPV 18	**Month 3**	381	211.3 (187.6, 238.0)	399	255.1 (227.8, 285.8)	372	270.1 (238.6, 305.8)	755	291.6 (270.3, 314.5)
	Month 7	385	**546.4** (483.4, 617.7)	408	**640.5** (570.8, 718.6)	384	**652.9** (577.0, 738.7)	769	**699.4** (644.2, 759.4)

Source: Table 7-1, CSR 016v2, p. 148

TABLE 193
Protocol 016- End-Expiry Substudy: Summary of the Proportions of Subjects who Became Seropositive to Vaccine HPV type by Group (PPI Population) at Month 3 and Month 7

		20% formulation N=503		40% formulation N=513		60% formulation N=508		100% formulation N=1017	
Assay	Time point	n	Seroconversion 95% CI	n	Seroconversion 95% CI	n	Seroconversion 95% CI	n	Seroconversion 95% CI
Anti-HPV 6	**Month 3**	372	99.7% (98.5, 100%)	384	100% (99.0, 100%)	359	99.4% (98.0, 99.9%)	732	100% (99.5, 100%)
	Month 7	375	100% (99.0, 100%)	393	100% (99.1, 100%)	370	99.7% (98.5, 100%)	746	100% (99.5, 100%)
Anti-HPV 11	**Month 3**	372	100% (99.0, 100%)	384	100% (99.0, 100%)	359	99,7% (98.5, 100%)	733	100% (99.5, 100%)
	Month 7	375	100% (99.0, 100%)	393	100% (99.1, 100%)	370	99.7% (98.5, 100%)	746	100% (99.5, 100%)
Anti-HPV 16	**Month 3**	365	100% (99.0, 100%)	368	99.7% (98.5, 100%)	358	100% (99.0, 100%)	721	99.9% (99.2, 100%)
	Month 7	368	100% (99.0, 100%)	377	100% (99.0, 100%)	370	99.7% (98.5, 100%)	733	100% (99.5, 100%)
Anti-HPV 18	**Month 3**	381	95.3% (92.6, 97.2%)	399	97.2% (95.1, 98.6%)	372	97.3% (95.1, 98.7%)	755	98.3% (97.1, 99.1%)
	Month 7	385	99.7% (98.6, 100%)	408	99.3 % (97.9, 99.8%)	384	99.0% (97.4, 99.7%)	769	99.6% (98.9, 99.9%)

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for the HPV 6, 11, 16, and 18 cLIAs were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Subjects with anti-HPV GMTs $\geq$ the levels above were considered to be seropositive.
Source: Table 7-2, CSR 016v2, p. 149

- **Comparison of anti-HPV serum cLIA responses**
  - The conclusion was that the 20% formulation was the minimum acceptable end-expiry formulation, both by GMT ratios being between 0.5 and 2.0 (Primary analysis), and the seroconversion rates showing a difference < 5% (secondary analysis).

TABLE 194
Protocol 016: Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA GMTs Between Subjects who Received Partial Dose Formulations and those who Received Full Dose Formulations (PPI Population)

		Comparison Group A (Partial Dose Group)			Comparison Group B (Full Dose Group)			Estimated Fold difference Group A/Group B 95% CI	p-value for non-inferiority
Assay (cLIA)	Comparison Group A vs. Comparison Group B	N	n	Estimated GMT mMU/mL	N	n	Estimated GMT mMU/mL		
Anti-HPV 6	20% v. 100%	503	375	553.1	1017	746	751.6	0.74 (0.66, 0.83)	< 0.001
	40% vs. 100%	513	393	661.4	1017	746	754.7	0.88 (0.78, 0.98)	< 0.001
	60% vs. 100%	508	370	666.1	1017	746	751.3	0.89 (0.79, 1.00)	< 0.001
Anti-HPV 11	20% vs. 100%	503	375	596.6	1017	746	935.5	0.64 (0.56, 0.72)	< 0.001
	40% vs. 100%	513	393	748.3	1017	746	941.7	0.79 (0.70, 0.90)	< 0.001
	60% vs. 100%	508	370	777.8	1017	746	937.0	0.83 (0.73, 0.94)	< 0.001
Anti-HPV 16	20% vs. 100%	503	368	2258.9	1017	733	3527.1	0.64 (0.55, 0.75)	0.001
	40% vs. 100%	513	377	2643.8	1017	733	3542.5	0.75 (0.64, 0.87)	< 0.001
	60% vs. 100%	508	370	2868.3	1017	733	3518.5	0.82 (0.70, 0.95)	< 0.001
Anti-HPV 18	20% vs. 100%	503	385	518.7	1017	769	656.3	0.79 (0.69, 0.91)	< 0.001
	40% vs. 100%	513	408	604.8	1017	769	656.7	0.92 (0.80, 1.06)	< 0.001
	60% vs. 100%	508	384	608.0	1017	769	653.0	0.93 (0.81, 1.07)	< 0.001

Group A received partial dose formulations and Group B received 100% dose formulations. N=Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis. Source: Table 7-3, CSR 016v2, p. 160

TABLE 195
Protocol 016: Statistical Analysis of Non-Inferiority Comparing Proportions of Subjects who Seroconverted at Month 7 Between Subjects who Received Partial Dose Formulations and Full Dose Formulations (PPI Population)

		Comparison Group A (Partial Dose Group)			Comparison Group B (Full Dose Group)			Estimated percentage point difference Group A-Group B 95% CI	p-value for non-inferiority
Assay (cLIA)	Comparison Group A vs. Comparison Group B	N	n	Estimated Response (%)	N	n	Estimated Response (%)		
Anti-HPV 6	20% v. 100%	503	375	100%	1017	746	100%	0.0 (-1.0,. 0.5)	< 0.001
	40% vs. 100%	513	393	100%	1017	746	100%	0.0 (-1.0, 0.5)	< 0.001
	60% vs. 100%	508	370	99.7%	1017	746	100%	-0.3 (-1.5, 0.3)	< 0.001
Anti-HPV 11	20% vs. 100%	503	375	100%	1017	746	100%	0.0 (-1.0, 0.5)	< 0.001
	40% vs. 100%	513	393	100%	1017	746	100%	0.0 (-1.0, 0.5)	< 0.001
	60% vs. 100%	508	370	99/7%	1017	746	100%	-0.3 (-1.5, 0.3)	< 0.001
Anti-HPV 16	20% vs. 100%	503	368	100%	1017	733	100%	0.0 (-1.0, 0.5)	< 0.001
	40% vs. 100%	513	377	100%	1017	733	100%	0.0 (-1.0, 0.5)	< 0.001
	60% vs. 100%	508	370	99.7%	1017	733	100%	-0.3 (-1.5, 0.3)	< 0.001
Anti-HPV 18	20% vs. 100%	503	385	99.7%	1017	769	99.6%	0.1 (-1.1, 0.9)	< 0.001
	40% vs. 100%	513	408	99.3%	1017	769	99.6%	-0.3 (-1.8, 0.5)	< 0.001
	60% vs. 100%	508	384	99%	1017	769	99.6%	-0.6 (-2.3, 0.3)	< 0.001

Seroconversion = change in serostatus from seronegative to seropositive. The cut-offs for the HPV 6, 11, 16, and 18 cLIAs were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively. Group A received partial dose formulations and Group B received 100% dose formulations. N=Number of subjects randomized to the respective vaccination group who received at least 1 injection. n = Number of subjects contributing to the analysis. Source: Table 7-4, CSR 016v2, p. 161

- The results of statistical comparisons in the all HPV naïve with serology population were similar to those of the PPI analyses. (Source: Tables 11-20, 11-21, CSR -016v2, p. 334-5, not shown here)
- The results for GMTs and seroconversion rates are similar for the all HPV naïve with serology population. (Source: Tables 11-12, 11-13, CSR 016 v2, p. 318-9, not shown here)

- The GMTs are substantially higher for the 10-15 year old females as compared to the 16-23 year old females for each vaccine HPV type. The seroconversion rates are high in both age groups, although there was a slight dose response to HPV 18 in the older age group. (Source: Tables 11-14, 11-15, 11-16, 11-17, CSR 016v2, p. 320-3, not shown here).
- The sponsor has also presented the dose response curves for the 10-15 year old subjects separately from the 16-23 year old subjects. In the 10-15 year old age group, there is a consistent increase in GMTs with increasing doses of the vaccine, whereas in the 16-23 year old age group, the 60% formulation appears to provide a lower GMT as compared to the 40% formulation and the 100% formulation. (Source: Figures 11-1-11-8, p. 310-7, CSR 0-16v2; figures 11-3 and 11-7 shown below.)

Safety Evaluation-Adolescent Immunogenicity Substudy

- All subjects in this substudy received the full dose formulation.
- The overall proportion of subjects with at least 1 AE within 15 days of any vaccination was generally comparable among the 3 groups.
- The proportion of subjects with at least 1 injection-site adverse experience and the proportion of subjects with at least 1 systemic adverse experience were slightly higher among 16- to 23-year-old females compared with 10- to 15-year-old females and 10- to 15-year-old males. Among the 10- to 15- year-olds, males tended to have fewer injection-site adverse experiences and systemic adverse experiences than females.
- The proportions of subjects with any clinical adverse experience, any injection-site adverse experience and any systemic adverse experience were consistently lower among 10- to 15-year-old males compared with the females in both age categories following each of vaccination visits 1, 2, and 3.
- The proportions of subjects with any clinical adverse experience, any injection-site adverse experience, and any systemic adverse experience were generally higher following vaccination visit 1 than following vaccination visit 2 or 3. (Source: Tables 11-28, -29, -30, CSR 016v1, p. 302-4, not shown here)

TABLE 196
Protocol 016 - Adolescent Immunogenicity Substudy:
Clinical Adverse Experience Summary

	10-15 year old females N=506	10-15 year old males N=508	**16-23 year old females N=509**
Subjects with follow-up	501	500	497
N (%) with 1+ AE	455 (90.8%)	430 (86.0%)	456 (91.8%)
N (%) with IS AE	405 (80.8%)	370 (74.0%)	435 (87.5%)
N (%) with systemic AE	290 (57.9%)	256 (51.2%)	301 (60.6%)
N (%) with SAE	1 (0.2%)	1 (0.2%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)
D/C due to AE	1 (0.2%)	2 (0.4%)	0 (0.0%)
D/C due to SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: From Table 8-1, CSR 016v1, p. 177

Intensities of adverse events

- Within 15 days of any vaccination, slightly more of all 16-23 year old subjects with follow-up reported an AE that was moderate (41.9%) or severe (12.5%) as compared

to the 10-15 year old females (37.1% moderate and 10.8% severe) or the 10-15 year old males (31.2% moderate and 11.6% severe). (Source: Table 8-2, CSR 016v1, p. 179, not shown here)

- Among all reported adverse evenrs within 15 days after any vaccination, ≥ 94% of the reported AEs were mild or moderate in intensity, and more AEs were reported moderate in inensity by the 16-23 year old females (29.2%) as compared to the 10-15 year old females (26.0%) and males (22.8%). (Source: Table 8-3, CSR 016v1, p. 180, not shown here)

Injection Site AEs (Days 1-5 after any vaccination)

- In the 5 days after any vaccination, the most common injection site AE was pain in all three groups, followed by swelling and erythema.
- The proportions were generally comparable among the 3 groups, with the exception of injection site erythema and pain, which were somewhat higher in the 16-23 year old subjects as compared to the younger age groups.
- The young males had the lowest proportion of subjects with pain (71.4%) and erythema (18.6%), followed by the young females (79.4% pain and 20.2% erythema), followed by the 16-23 year old females (86.3% with pain and 26.2% with erythema). See Table 197 below.

TABLE 197
Protocol 016: Number (%) of Subjects With Injection Site AEs
(Days 1-5 Following Any Vaccination Visit)

	10-15 year old females N=506	10-15 year old males N=508	16-23 year old females N=509
	Gardasil	Gardasil	Gardasil
	N (%)	N (%)	N (%)
Number of subjects with follow-up	501	500	497
Number (%) with 1+ IS AE	403 (80.4%)	370 (74.0%)	435 (87.5%)
Injection Site Pain	398 (79.4%)	357 (71.4%)	429 (86.3%)
Injection Site Swelling	127 (25.3%)	107 (21.4%)	125 (25.2%)
Injection Site Erythema	101 (20.2%)	93 (18.6%)	130 (26.2%)
Injection Site Pruritis	13 (2.6%)	5 (1.0%)	10 (2.0%)
Injection Site Bruising	12 (2.4%)	8 (1.6%)	12 (2.4%)

Source: Table 8-4, CSR 016v1, p. 182

- In general, there was a higher number of subjects in all groups with complaints of injection site AEs after Dose 1 compared to Doses 2 and 3. The exception was injection site swelling, where there were higher proportions of subjects with this AE with progressive doses. (Source: Tables 11-35, -36, -37, CSR 016v1, p. 309-11, not shown here)

Comparison of Injection Site AEs

- Risk differences were compared for each injection site AEs in 16-23 year old women as compared to 10-15 year old females, and separately compared to 10-15 year old males.

- There were statistically higher incidences of injection site pain and erythema in the 16 – 23 year old females as compared to the 10-15 year old females (as well as males). (Source: Tables 8-5, 8-6, CSR 016v1, p. 184-5, not shown here)

Intensities of Injection Site AEs

- The majority of subjects judged the intensity of injection site AEs within 5 days after any vaccination to be mild in intensity.
- A higher proportion of 16-23 year old females judged an injection site AE to be moderate (27.8%) compared to the younger females (23.6%).
- A higher proportion of 10-15 year old females judged the injection site AE to be severe (4.4%) compared to the older females (3.8%) and males (3.0%). Source: Table 8-7, CSR 012v1, p. 187, not shown here)
- The frequency of severe injection site AEs across the groups was generally comparable for pain/tenderness/soreness and erythema. (Source: Table 8-11, CSR 016v1, p. 191, not shown here)

Systemic AEs (Days 1-15 after any vaccination)

- The proportion of systemic AEs in the 15 days after any vaccination was slightly higher among the 16-23 year old females (60.6%) compared to the 10-15 year old females (57.9%) or males (51.2%).
- The most common systemic AE in the 16-23 year old subjects was headache.
- The most common systemic AEs in the 10-15 year old subjects were headache and pyrexia.
- The proportion of 10-15 year old females with pyrexia (14.8%) was higher compared to those in the 16-23 year old subjects (8.5%). Males had the highest proportion with pyrexia (16.0%) (Source: Table 8-12, CSR 016v1, p. 193-5; and Table 11-53, p. 333-40, not shown here)
- Comparing the doses, there was a higher incidence of systemic AEs after dose 1 compared to doses 2 and 3 in all groups.
- Following dose 1 and 2, the proportion of systemic AEs in the 16-23 year old subjects 40.8% and 28.8%, respectively) was higher than in the 10-15 year old females (38.7% and 23.5%, respectively) and males (31.2% and 20.4%, respectively). The incidences were comparable in the 3 groups after Dose 3. (Source: tables 11-50, -51, -52, CSR 016v1, p. 327-32, not shown here)

Systemic AEs and baseline serostatus of subjects

- The proportion of subjects reporting systemic AEs were slightly lower in 16-23 year old subjects who were initially positive as compared to 16-23 year old subjects who were initially seronegative.
- The small number of 10-15 year old subjects who were initially seropositive make interpretation of these results more difficult. (Source: Tables 11-54, -55, -56, -57, CSR 016v1, p. 341-9, not shown here)

Comparison of systemic AEs between older females and younger females

- The comparison of systemic AEs in older and younger females is shown in Table 198 below.

TABLE 198

Protocol 016: Comparison of 10-15 year old Females and 16-23 year old Females with Respect to the Number (%) of Subjects who Reported Systemic Clinical AEs After Gardasil by System Organ Class (Days 1-15 Following Any Vaccination Visit)

	10-15 year old females N=506	16-23 year old females N=509
Number of subjects with f/u	501	497
Number (%) with 1+systemic AE	290 (57.9%)	301 (60.6%)
Ear Disorders	6 (1.2%)	1 (0.2%)
Ear pain	5 (1.0%)	0 (0.0%)
GI Disorders	83 (16.6%)	78 (15.7%)
Abdominal pain	15 (3.0%)	5 (1.0%)
Abdominal pain upper	17 (3.4%)	14 (2.8%)
Diarrhea	20 (4.0%)	10 (2.0%)
Nausea	18 (3.6%)	29 (5.8%)
Vomiting	19 (3.8%)	8 (1.6%)
General Disorders	98 (19.6%)	70 (14.1%)
Asthenia	4 (0.8%)	5 (1.0%)
Fatigue	11 (2.2%)	18 (3.6%)
Malaise	5 (1.0%)	5 (1.0%)
Pyrexia	74 (14.8%)	42 (8.5%)
Immune System Disorders	3 (0.6%)	5 (1.0%)
Infections	88 (17.6%)	90 (18.1%)
Injury	19 (3.8%)	8 (1.6%)
MS and Connective Tissue Disorders	38 (7.6%)	46 (9.3%)
Arthralgia	12 (2.4%)	7 (1.4%)
Myalgia	7 (1.4%)	13 (2.6%)
Nervous System Disorders	120 (24.0%)	153 (30.8%)
Dizziness	8 (1.6%)	24 (4.8%)
Headache	111 (22.2%)	138 (27.8%)
Psych Illnesses	5 (1.0%)	15 (3.0%)
Reproductive System and Breast Disorders	16 (3.2%)	40 (8.0%)
Respiratory Disorders	40 (8.0%)	42 (8.5%)
Skin Disorders	11 (2.2%)	14 (2.8%)

Source: Table 8-13, CSR 016v1, p. 196-198

- Males 10-15 years of age had a lower proportion of systemic AEs as compared to girls 10-15 years of age. (Source: Table 8-14, CSR 016v1, p. 197-200, not shown here)

Intensities of systemic AEs

- A higher proportion of 16-23 year old females (31.6%) reported that their worst systemic AE were moderate in intensity compared to the 10-15 year old females (25.1%) and males (21.4%). (Source: Table 8-15, CSR 016v1, p. 202, not shown here)
- Within each group, app. 90% of the reported systemic AEs were mild to moderate in intensity.
- The 16-23 year old females tended to report more systemic AEs that were moderate in intensity (47.3%) compared to the 10-15 year old females (40.3%) and males (36.5%). (Source: Table 8-16, CSR 016v1, p. 203, not shown here)

- When assessed after dose 1, 2, and 3, the distribution of systemic AEs by maximum intensity appeared comparable to vaccinations overall. (Source: Tables 1-59, -60, -61, CSR 016v1, p. 357-68, not shown here)

Temperatures (Days 1-5 after any vaccination)

- In the 5 days after any vaccination, more subjects in the 10-15 year old subjects reported a fever (defined as a T $\geq$ 37.8 deg C) compared with the 16-23 year old subjects. Very few reported a T $\geq$ 39.9 deg C.

TABLE 199
Protocol 016: Number (%) of Subjects with Elevated Temperatures
(Days 1-5 Following Any Vaccination Visit)

	10-15 year old females N=506	10-15 year old males N=508	**16-23 year old females N=509**
Subjects with follow-up	499	500	493
Maximum T			
< 37.8 deg C (100 deg F)	435 (87.2%)	431 (86.2%)	457 (92.7%)
$\geq$ 37.8 deg C and < 38.9 deg C (102 deg F)	53 (10.6%)	52 (10.4%)	32 (6.5%)
$\geq$ 39.9 deg C and < 39.9 deg C (103.8 deg F)	9 (1.8%)	14 (2.8%)	3 (0.6%)
$\geq$ 39.9 deg C and < 40.9 deg C (105.6 deg F)	1 (0.2%)	3 (0.6%)	1 (0.2%)
$\geq$ 40.9 deg C (105.6 deg F)	1 (0.2%)	0 (0.0%)	0 (0.0%)

Source: Table 8-17, CSR 016v1, p. 204

- The proportions of subjects who reported a fever were comparable postdose 1, postdose 2, and postdose 3. The proportions of subjects who reported a T at or above 39.9 deg C were comparable postdose 1, 2, and 3. (Source: Tables 11-62, -63, -64, -65, -66, -67, CSR 016v1, p. 369-74, not shown here)
- A statistical comparison of pyrexia between the 10-15 year old subjects and the 16-23 year old females was provided. Female subjects 10-15 years of age had a higher risk of developing lower grade Temperatures (< 102 deg F, oral) as compared to females 16-23 years of age. There was no increased risk for development of Temperatures > 102 deg F, oral, in the younger females as compared to the older females. (See Table 200 below.)

TABLE 200
Protocol 016: Risk Differences for Fever in 10-15 year old Females Compared to 16-23 year old Females

	10-15 year old females N=506	16-23 year old females N=509	Risk Difference (10-15 year old females – 16-23 year old females)	95% CI
Subjects with follow-up	499	493		
Maximum T				
< 37.8 deg C (100 deg F)	435 (87.2%)	457 (92.7%)	NA	NA
≥ 37.8 deg C (100 deg F)	**64 (12.8%)**	**36 (7.3%)**	**5.5**	**(1.8, 9.3)**
≥ 37.8 deg C and < 38.9 deg C (102 deg F)	**53 (10.6%)**	**32 (6.5%)**	**4.1**	**(0.7, 7.7)**
≥ 39.9 deg C and < 39.9 deg C (103.8 deg F)	9 (1.8%)	3 (0.6%)	1.2	(-0.2, 2.9)
≥ 39.9 deg C and < 40.9 deg C (105.6 deg F)	1 (0.2%)	1 (0.2%)	0.0	(-1.0, 0.9)
≥ 40.9 deg C (105.6 deg F)	1 (0.2%)	0 (0.0%)	0.00	(-0.6, 1.1)

Source: Amendment 0017, Safety Information Amendment 3/30/06, Response to Question 3

- The proportion of subjects in the 10-15 year old male group with an elevated temperature was also statistically higher compared to the 16-23 year old subjects. (Source: Tables 8-20, CSR 016v1, p. 207, not shown here)

Temperature elevation and baseline HPV status

- A higher proportion of 16-23 year old subjects who were baseline HPV positive reported a fever compared to those who were baseline negative. The small size of baseline HPV positive subjects in the 10-15 year old age group makes interpretation more difficult, although a higher proportion of subjects in the 10-15 year old age group who were non-naïve to HPV types had a Temperature as compared to the naïve subjects in the 10-15 year old subjects. (Source: Tables 11-68, -69, -70, -71, CSR 016v1, p. 375-8, not shown here)

Significant/Potentially Significant Events
Deaths: One

- **AN 64196:** 15 year old white male who received the vaccine, was reported to have had a **ventricular arrhythmia** 27 days after receipt of Dose 2. The autopsy was inconclusive (although there was a suspicion that the subject had an aneurysm). Additional information was requested from the sponsor, which indicated that there was a family history for cardiac arrhythmia (mother, sister, uncle), and that the subject was driving a go-cart at the time of the event. The assessment by the sponsor was that the subject suffered from an epinephrine-driven ventricular fibrillation. The subject's drug screen was negative. (Source: Amendment 0017, Safety Information Amendment, Protcol 016, Question 1, 3/30/06).

SAEs: There were three SAEs reported. (See Table 201 below.) (There were no placebo recipients in this study.)

TABLE 201
Protocol 016 - Adolescent Immunogenicity Substudy: SAEs in Vaccinees

AN	Age	Event	Days after dose	Duration	Recovered
62075	13 year old female	Vaginal bleeding	26 days postdose 1 42 days postdose 3 125 days postdose 3	1 month 7 days 9 days	Yes Received hormonal therapy
62247	15 year old female	Intentional overdose	13 days postdose 2	1 day	Recovered
64123	15 year old male	Lower abdominal pain, vomiting, diarrhea	9 days postdose 1	2 days	Recovered

Source: From Table 8-22, CSR 016v1, p. 212

Discontinued further vaccinations due to a nonserious AE: Five

- **AN 62059:** 14 year old Asian female received the vaccine and discontinued postdose 1 due to **injection site AE pain** of mild intensity. She also experienced **vomiting** postdose 1. **Investigator attribution**: AE was probably related to the study vaccine.
- **AN 64366:** 14 year old Asian male received the vaccine due to a **rash** of moderate intensity 1 day postdose 1. Another AE was **redness at the injection site**. This subject discontinued from further vaccination but continued in the follow-up part of the study. **Investigator Attribution:** related to the vaccine.
- **AN 64556:** 13 year old white male discontinued from the study 4 days postdose 1 due to **diarrhea** of moderate intensity and **swollen cervical lymph** nodes 8 days postdose 1. Another AE was injection site pain.**Investigator Attribution:** probably not related to study vaccine.
- **AN 61116:** 18 year old Hispanic female discontinued 40 days postdose 2 due to **Rheumatoid Arthritis. Investigator attribution:** possibly related to the study vaccine. Additional information was requested. This subject developed left wrist pain approximately 1 month after dose 2 of Gardasil. This pain resolved, but she then developed left shoulder pain. Over the next few months, the pain involved her wrists, shoulders, knees, ankles, toes and left hips. She experienced morning stiffness. There was no response to ibuprofen. Family history was significant for hypothyroidism in her mother and sister, and fibromyalgia and chronic fatigue syndrome in her mother; there was no history of SLE or RA. She was seen by a pediatric rheumatologist app. 3 months after the start of the synptoms. On joint examination, she had mild swelling in the right PIP joint of her thumb and left great toe (as well as MTP of left great toe). She was started on naprosyn. Lab tests showed a C-reacttive protein of 1.8 mg/dL, an ESR of 35 mm/hr, and a mildly positive RF of 22. On naprosyn, her symptoms decrased but did not resolve totally, and her ESR and C-reactive protein decreased to normal. She was started on methotrexate and tapering prednisone, with continuation of naprosyn. Her disease went into medical remission, and she continues on the methotrexate (as well as Yasmin oral contraceptive and zantac and folic acid).

Reviewer's Comment: See Safety overall for discussion of incidence of autoimmune events and the comparison to the general population.

Pregnancy Outcomes

- One infant developed an AE during the study period. (See End Expiry substudy safety results below).

New Medical History

- A slightly lower proportion of 10-15 year old males and females than 16-23 year old females reported a new medical condition in the Day 1 through Month 7 period.
- The most common new medical conditions among the 16-23 year old females were infections (mostly upper respiratory infections), followed by nervous system disorders (mostly headache).
- The most common new medical conditions among the 10-15 year olds were infections (mostly upper respiratory infections) followed by injuries. (Source: Tables 8-30, 8-31, p. 222-6; and Tables 11-72, 11-73, p. 379-92, CSR 016v1, not shown here)

Safety Evaluation: End Expiry Substudy

Table 202 below provides the clinical adverse event summary for subjects participating in the End Expiry substudy.

TABLE 202
Protocol 016 - -End Expiry Substudy: Clinical Adverse Experience Summary – Days 1-15 after any vaccination

	20% formulation N=503	40% formulation N=514	60% formulation N=507	100% formulation N=1015
Subjects with follow-up	496	509	500	998
N (%) with 1+ AE	444 (89.5%)	443 (87.0%)	441 (88.2%)	911 (91.3%)
N (%) with IS AE	408 (82.3%)	406 (79.8%)	402 (80.4%)	840 (84.2%)
N (%) with systemic AE	291 (58.7%)	294 (57.8%)	304 (60.8%)	591 (59.2%)
N (%) with SAE	3 (0.6%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Deaths	0	0	0	0
D/C due to AE	2 (0.4%)	0	1 (0.2%)	1 (0.1%)
D/C due to SAE	1 (0.2%)	0	0	0

Source: From Table 8-1, CSR 016v2 p. 166-7

- The overall proportions of subjects with AEs were comparable among the 4 groups.

Injection Site AEs (Day 1-5 after any vaccination)

- The most common injection site AE was pain, followed by erythema and swelling. (Source: Table 8-2, p. 169, and Table 11-31, p. 351-2, not shown here)
- The proportions of subjects with a specific injection site AE were generally comparable in the 4 groups.
- The proportions of subjects with specific injection site AEs were reported after each dose of vaccine and were comparable among the 4 groups. However, a slightly higher proportion of subjects reported erythema and swelling after doses 2 and 3 compared to after dose 1. (Source: Tables 11-28, 11-29, 11-30, CSR 016v2, p. 348-50, not shown here)
- There was a slightly higher proportion of injection site AEs reported by the 16-23 year old age group in the 20% and 100% formulations as compared to the 10-15 year old age group. (Source: Tables 11-32, 11-33, CSR 016v2, p. 353-5, not shown here)

Systemic AEs (Days 1-15 days after any vaccination)

- The most common systemic AEs were headache and pyrexia, and the proportions of subjects reporting these AEs were comparable among the 4 groups. Two other more common systemic AEs were nausea and nasophrayngitis. (Source: Table 8-3, p. 171-5, and Table 11-37, p. 370-93, CSR 016v2, not shown here)
- Systemic AEs were reported less frequently after doses 2 and 3 compared to after dose 1. (Source: Tables 11-34, -35, -36, p. 356-69, not shown here)
- A higher proportion of the 10-15 year old females (12-17%) had report of pyrexia as compared to the 16-23 year old females (9-12%).
- A higher proportion of the 16-23 year old subjects (60-64%) had report of a systemic AE as compared to the 10-15 year old subjects (54-58%).
  (Source: Table 11-38, 11-39, CSR 016v2, p. 394-406, not shown here)

Temperatures (Days 1-5 after any vaccination)

- The proportions of subjects with elevated Ts were comparable among the 4 dose groups.
- There were no apparent differences in the proportions of subjects with elevated Ts after doses 1, 2, and 3. (Source: Tables 11-40, -41, -42, CSR 016v2, p. 407-9, not shown here)

TABLE 203
Protocol 016: End-Expiry Substudy: Number (%) of Subjects with Elevated Temperatures (Days 1-5 Following Any Vaccination Visit)

	20% formulation N=503	40% formulation N=514	60% formulation N=507	100% formulation N=1015
Subjects with follow-up	494	507	494	992
Maximum T				
< 37.8 deg C (100 deg F)	431 (87.2%)	445 (87.8%)	451 (91.3%)	892 (89.9%)
≥ 37.8 deg C and < 38.9 deg C (102 deg F)	54 (10.9%)	56 (11.0%)	37 (7.5%)	85 (8.6%)
≥ 39.9 deg C and < 39.9 deg C (103.8 deg F)	7 (1.4%)	5 (1.0%)	6 (1.2%)	12 (1.2%)
≥ 39.9 deg C and < 40.9 deg C (105.6 deg F)	2 (0.4%)	1 (0.2%)	0 (0.0%)	2 (0.2%)
≥ 40.9 deg C (105.6 deg F)	0	0	0	1 (0.1%)

Source: Table 8-4, CSR 016v2, p. 177

- The sponsor also presents the 10-15 year old age group separately from the 16-23 year old age group. Higher proportions of the 10-15 year old subjects had an elevated T compared to the 16-23 year old age group. (See Tables 204 and 205 below.)

TABLE 204
Protocol 016 – End Expiry Substudy: Number (%) of Subjects with Elevated Temperatures (Days 1-5 Following Any Vaccination Visit) – 16-23 year old age group

	20% formulation N=251	40% formulation N=259	60% formulation N=256	100% formulation N=509
Subjects with follow-up	243	253	244	493
Maximum T				
< 37.8 deg C (100 deg F)	220 (90.5%)	223 (88.1%)	224 (91.8%)	457 (92.7%)
≥ 37.8 deg C and < 38.9 deg C (102 deg F)	21 (8.6%)	26 (10.3%)	17 (7.0%))	32 (6.5%)
≥ 39.9 deg C and < 39.9 deg C (103.8 deg F)	2 (0.8%)	4 (1.6%)	3 (1.2%)	3 (0.6%)
≥ 39.9 deg C and < 40.9 deg C (105.6 deg F)	0	0	0	**1 (0.2%)**
≥ 40.9 deg C (105.6 deg F)	0	0	0	0

Source: Table 11-46, CSR 016v2, p. 413

TABLE 205
Protocol 016- End Expiry Substudy: Number (%) of Subjects with Elevated Temperatures (Days 1-5 Following Any Vaccination Visit) – 10-15 year old female age group

	20% formulation N=252	40% formulation N=255	60% formulation N=251	100% formulation N=506
Subjects with follow-up	251	254	250	499
Maximum T				
< 37.8 deg C (100 deg F)	211 (84.1%)	222 (87.4%)	227 (90.8%)	435 (87.2%)
≥ 37.8 deg C and < 38.9 deg C (102 deg F)	33 (13.1%)	30 (11.8%)	20 (8.0%)	53 (10.6%)
≥ 39.9 deg C and < 39.9 deg C (103.8 deg F)	5 (2.0%)	1 (0.4%)	3 (1.2%)	9 (1.8%)
≥ 39.9 deg C and < 40.9 deg C (105.6 deg F)	2 (0.8%)	1 (0.4%)	0	**1 (0.2%)**
≥ 40.9 deg C (105.6 deg F)	0	0	0	**1 (0.2%)**

Source: Table 11-48, CSR 016v2, p. 415

Significant/Potentially Significant Events

Deaths: none.

SAEs: There were ten SAEs reported. (See Table 206 below.) (There were no placebo recipients in this study.)

TABLE 206
Protocol 016 –End Expiry Substudy: SAEs in Vaccinees

AN	Age	Event	Days after dose	Duration	Recovered	Action taken
20% formulation						
62825	14 yrs.	Severe AE to phencyclidine hydrochloride (PCP)	5 days postdose 2	2 days	yes	None
60643	16 yrs.	Failed trial of labor	279 days postdose 2	5 days	yes	Did not receive dose 3
60263	23 yrs.	Convulsion – vasovagal syncope	12 days postdose 2	10 minutes	Yes	Continued in study
63036	15 yrs.	Hyperemesis gravdium	192 days postdose 2	3 days	Yes	**Did not receive dose 3 yet**
63354	13 yrs.	Anorexia nervosa (severe) – had history of eating disorder	15 days postdose 2	CONT	No	**No further vaccine**
40% formulation						
60778	20 yrs.	CPD, PROM	245 days postdose 3	8 hours	Yes	**N/A**
60116	21 yrs.	Pyrexia, tachycardia fetal (subject pregnant)	280 days postdose 3	1 day	Yes	**N/A**
60% formulation						
61156	17 yrs.	Convulsion On multiple psych meds	14 days postdose 3	15 minutes	Yes	**N/A**
100% formulation						
62075	13 yrs.	Vaginal hemorrhage Vaginal hemorrhage	26 days postdose 1 42 days postdose 3	1.71 mos. 2.3 mos.	Yes	**Received 3 doses**
62247	14 yrs.	Intentional OD	13 days postdose 2	2 days	Yes	Received 3 doses

Source: Table 8-6, CSR 016v2, p. 180-1

Subjects who discontinued due to AE: 5 subjects

- **AN 61116:** 18 year old Hispanic female **with RA** 40 days after receiving dose 2 of the 100% formulation (details are provided above). This was considered moderate in intensity by the investigator.
- **AN 60403:** 18 year old black female developed a **moderate skin reaction** 1 day after dose 1 of the 20% dose formulation, which lasted 5 days. She did not receive further vaccine.
- **AN 62059:** 14 year old Asian female who received 100% dose formulation and developed **injection site pain** 1 days after dose 1 and moderate vomiting at 5 days after dose 1 (which lasted 2 days).
- **AN 62020:** 12 year old white female who received 60% dose formulation and developed **severe tonsillitis** at 2 days after dose 1 (lasting 19 days) and **severe nausea**

at 4 days after dose 1 (lasting 8 days). Other AEs included injection site pain, nausea, and pyrexia.

- **AN 63354:** 13 year old white female received 20% dose formulation and discontinued from the study at 15 days after dose 2 due to anorexia nervosa. As noted above, there was a history of an eating disorder prior to vaccination.

Pregnancy Outcomes

- Overall, 1.18% (30/2539) of the cohort became pregnant during the study.
- The outcomes of 26/30 pregnancies are known: 18 resulted in a live birth of a normal baby, 2 resulted in a spontaneous abortion, and 6 resulted in elective termination of pregnancy.

TABLE 207
Protocol 016 – End Expiry Substudy: Pregnancy Outcome Summary

	20% formulation N=503	40% formulation N=514	60 % formulation N=507	100% formulation N=1015
Subjects with Pregnancies	5 (1.0%)	7 (1.4%)	7 (1.4%)	11 (1.1%)
Number of pregnancies	5	7	7	11
Number of pregnancies with unknown outcome	1	0	0	3
Number of fetuses/infants with known outcome	4	7	7	8
Live Births	2 (50.0%)	5 (71.4%)	5 (71.4%)	6 (75.0%)
Infant Outcome				
Normal	2 (100.0%)	5 (100.0%)	5 (100.0%)	6 (100.0%)
Abnormal	0	0	0	0
Unknown	0	0	0	0
Fetal Loss	2 (50.0%)	2 (28.6%)	2 (28.6%)	2 (25.0%)
Spontaneous Abortion*	1 (50.0%)	0	0	1(50.0%)
Late Fetal Death	0	0	0	0
Elective Abortion*	1 (50.0%)	2 (100.0%)	2 (100.0%)	1 (50.0%)
Fetal Outcome				
Normal	0	0	0	0
Abnormal	0	0	0	0
Congenital Anomaly	0	0	0	0
Other medical condition	0	0	0	0
Unknown	0	0	0	0

*Percentages based on number of fetal losses.
Source: Table 8-8, CSR 016v2, p. 191-2

- There were no congenital anomalies.
- Two **SAEs were reported in infants** during the study period. (See Table 208 below.)

TABLE 208
Protocol 016: SAEs in Infants Born to Vaccinees

AN of mother	Event in infant	Days postdose event occurred + formulation	Duration	Outcome
61292	Meningitis, sepsis	200 days postdose 2 (60% formulation)		Fatal
60574	Pneumonia	20 days postdose 2 (100% formulation)	5 days	Recovered

Source: Table 8-9, CSR 016v2, p. 193 and narratives from p. 189-90

New Medical Condition

- The proportions of subjects reporting a new medical condition in the 7 month vaccination period were comparable among the groups.
- The most common new medical conditions reported were infections (mostly upper respiratory infections) and headaches. (Source: Table 8-10, p. 195-98; Table 11-50, p. 417-43, not shown here, CSR 016v2)

Comments-Conclusion Regarding Data for Protocol 016 (Reviewer's Opinion)

- Protocol 016 had 2 substudies: the Adolescent Immunogenicity substudy and the End Expiry substudy.
- This was the first trial in which children 10-15 years of age received the quadrivalent HPV vaccine.

- **Safety**
  - The vaccine was administered to 10-15 year old girls and boys, as well as 16-23 year old females in the Adolescent Immunogenicity Substudy at 100% formulation, and safety was compared between the younger age groups and the 16-23 year old age group.
  - In general, the younger subjects had a lower incidence of any adverse event (both injection site and systemic event) compared with the 16-23 year old subjects in the 15 days after any vaccination.
  - The only exception was that the 10-15 year old subjects had a higher incidence of temperature elevation in the 5 days after any vaccination compared with the 16-23 year old subjects. Most of the Ts that occurred in all groups (10.4%-10.6% of the young girls and boys, respectively as compared to app. 6.8% in the 16-23 year old females) were < 102 deg F. 3% of the 10-15 year old males and 2% of the 10-15 year old females had Ts $\underline{\geq}$ 102 deg F to < 103.8 deg F.
  - The most common injection site AEs were pain, swelling, and erythema.
  - The most common systemic AE was headache in 16-23 year old females, and headaches and pyrexia in the 10-15 year old groups.
  - The majority of AEs were mild to moderate in intensity. In general, there was a higher proportion of subjects with an AE after Dose 1 as compared to Dose 2 and Dose 3.
  - There was a slightly lower proportion of 16-23 year old subjects with an injection site or systemic AE who were non-naïve to a vaccine HPV type compared to those who were naïve to a vaccine HPV type. There were too few 10-15 year old subjects who were non-naïve to a vaccine HPV type to make an assessment regarding this matter.

- One SAE of interest involved a 15 year old male who died of a ventricular arrythmia 27 days postdose 1. The autopsy was inconclusive, but there was a strong family history of arrhythmia.
- An 18 year old female developed rheumatoid arthritis 40 days after the second dose of the quadrivalent vaccine. An overview of immune mediated AEs are noted in the overall safety summary.
- No safety issues were identified, but it is noted that safety data from the 100% formulation recipients were those of interest.
- In this substudy, there was one 27 year old subject who experienced a seizure 12 days after the second dose of 20% formulation (and was diagnosed with vasovagal syncope).
- One child born to a mother who received the 60% formulation app. 200 days following dose 2 died of meningitis (infectious agent not stated) and sepsis soon after birth. One other child, who was breast-feeding, developed pneumonia at 20 days after his mother received dose 2 of the vaccine, and recovered after 5 days.
- In protocol 016, the rate of spontaneous abortions was low, and there were no congenital abnormalities.

- **Immunogenicity**
  - **Adolescent Immunogenicity Substudy**
    - The immune response to the quadrivalent vaccine at Month 7 in 10-15 year old females was non-inferior to the immune response in 16-23 year old women. This was assessed by comparison of GMT ratios (ruling out a decrease > 2-fold GMTs) and assessing the difference in seroconversion rates (ruling out a difference > 5%). Immune responses in 10-15 year old males were also non-inferioir as compared to immune responses in 16-23 year old females.
    - 10-15 year olds who received the 100% formulation received the same lot as the 16-23 year old subjects. These 16-23 year old subjects were not the same subjects as participated in the Protocols 013 or 015, the efficacy studies, and the lot used as the 100% formulation was not the same one used in the efficacy studies.
    - In subjects 16-23 years of age who were non-naïve to vaccine HPV types at baseline, there were higher GMTs at Month 3 and 7 compared to those who were naïve to vaccine HPV types at baseline.
  - **End Expiry Substudy**
    - There was a general dose response for the vaccine HPV types with increasing dose formulations of the quadrivalent vaccine. The conclusion was that the 20% formulation was the minimum acceptable end expiry formulation because of the non-inferiority of GMTs primarily (ruling out > 2 fold decrease in GMT ratios), and secondarily by ruling out a difference > 5% in seroconversion rates between the comparison groups.
    - The sponsor believed that this End Expiry substudy with this new product was important, although CBER cautioned early on that using immune responses to specific dilutions of vaccine may not predict the immune responses to specific dilutions of vaccine that aged during a normal shelf life. Nonetheless, all 4 vaccine formulations (20%, 40%, 60%, 100%) were immunogenic.

- The originally planned follow-up in the study was to be 1 month postdose 3 (Month 7). In a response to a regulatory agency, the total follow-up in Protocol 016 was 6 months postdose 3 (Month 12) in approximately 25% of subjects 10-15 years of age.

8.1.6: Trial #6

Protocol 018: A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents

Study Period: 10/8/03-1/19/05

Clean file achieved 1/31/05, and the database was unblinded on 2/2/05.

Protocol 018 Objectives

Primary Safety Objective

- To demonstrate that a 3-dose regimen of quadrivalent HPV vaccine is generally well tolerated in adolescents and preadolescents.

Secondary Immunogenicity Objectives

- To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls (by GMTs and seroconversion). Seroconversion is a change in serostatus from seronegative to seropositive. The anti-HPV serum cLIA cut-offs for determining serostatus are 20, 16, 20 and 24 mMU/mL for types HPV 6, 11, 16, and 18, respectively.
- To describe the persistence of immune response to the quadrivalent HPV vaccine, when given in a 3-dose regimen.

Design:

- Randomized, double-blind, placebo controlled, multicenter study in **9-15 year old** subjects.
- Enrollment was stratified by age and gender. Subjects were to be enrolled into 2 age strata (9 to 12 years of age and 13 to 15 years of age) in approximately a 2:1 ratio.
- The ratio of enrolled boys to girls was to be approximately 1:1. Approximately 1650 subjects were to be randomized in a 2:1 ratio to receive either quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or nonaluminum-containing placebo. Randomization was stratified by study center only.

TABLE 209
Protocol 018: Treatment Plan

Group	Quadrivalent HPV Vaccine	Non-alum Placebo
9-15 year old girls	550	225
9-15 year old boys	550	225
Total	1100	550

TABLE 210
Protocol 018: Vaccine Products Used

Clinical Material	Formulation Number	Dosage	Package and Storage
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI025T004	40/80/80/40 mcg plus 225 mcg aluminum adjuvant /mL 0.5 mL	0.75-mL single dose vial
Placebo for Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	PV501 VAI036P001	Carrier Solution Only /0.5 mL	0.75-mL single dose vial

HPV = Human papillomavirus; VLP = Virus-like particles.

Population: Protocol 018 was conducted in 47 sites in 10 countries in North America (US), Latin America (Colombia, Mexico), Europe (UK, Portugal, Norway, Denmark, Spain) and Asia (Thailand, Taiwan). The subjects were to be healthy preadolescents and adolescents who are not sexually active.

For full Inclusion and Exclusion Criteria, see APPENDIX 17

Vaccination schedule: Subjects received vaccine or placebo (0.5 mL) IM at 0, 2, and 6 months.

Concomitant Vaccines: None planned.

Endpoints
Primary Immunogenicity Endpoints
- Anti-HPV 6, 11, 16, 18 GMTs Week 4 postdose 3
- Pecentage of subjects who seroconverted (change in serostatus from seronegative to seropositive) for each of the vaccine HPV types by Week 4 postdose 3. Seropositive is defined as anti-HPV serum cLIA levels 20, 16, 20, 24 mMU/mL for HPV types 6, 11, 16, and 18, respectively.

Primary Safety Endpoints
- Occurrence of severe injection site AEs
- Incidence of any VR related SAE

TABLE 211
Protocol 018: Study Flow Chart

Event/Test	Consent Visit (Day 1)	Visit 2 Month 2	Visit 3 Month 6	Visit 4 Month 7	Visit 5 Month 12 Telephone Call	Visit 6 Month 18
Information brochure/prescreening	X					
Informed consent	X					
Medical History/PE	X					X
Pregnancy Test	X	X	X			
Serum for antibody measurements						
Anti-HPV 6, 11, 16, 18 cLIA	X			X		X
Retention serum, stored frozen at site	X			X		X
Vaccination	X	X	X			
Clinical follow-up for safety	X	X	X	X	X	X

Source: Table 5-1, CSR -18v1, p. 54

Special Procedures

- Because the true placebo was visually distinguishable from the HPV vaccine, an unblinded staff member was responsible for preparation and administration of the vaccine to the subject. The unblinded staff member retrieved the material from the storage site, made sure the allocation number was correct, and administered the vaccine. As soon as the vaccine was administered, the unblinded staff member left the room and a blinded staff member took over. These blinded staff members were responsible for monitoring the subjects after product administration and collection of all data and information from subjects and parents.
- The procedures were as noted for Protocol 013 and 016 for 10-15 year old subjects (except that in this protocol, there was no 3 month visit, and there was an additional 18 month visit as compared to Protocol 016). The BLA contains data out to 1 month postdose 3 (Month 7). There was a separate report for safety data out to Month 12. Additional safety data will be submitted for 6 and 12 months postdose 3 in separate reports in the future.

Statistical Considerations

- **Immunogenicity Objectives**
  - To show that the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces noninferior immune responses with respect to each of the vaccine components individually in preadolescent/adolescent boys who are seronegative to the relevant HPV type at Day 1, relative to preadolescent/adolescent girls who are seronegative to the relevant HPV type at Day 1, as measured by the **GMTs** to HPV 6, 11, 16, and 18 at Week 4 Postdose 3.
  - To show that the quadrivalent HPV vaccine induces noninferior immune responses with respect to each of the vaccine components individually in preadolescent/adolescent boys who are seronegative to the relevant HPV type at Day 1, relative to preadolescent/adolescent girls who are seronegative to the relevant HPV type at Day 1, as measured by the percentages of subjects who **seroconvert** (change in serostatus from seronegative to seriopositive) for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3. Seropositive is defined as

anti-HPV serum cLIA levels ≥ 20, 16, 20, 24 mMU/mL for HPV types 6, 11, 16, and 18, respectively.

- In order to declare the immune responses of boys to the quadrivalent HPV vaccine at Week 4 Postdose 3 noninferior to those of girls, the statistical criterion had to be met for each HPV type and for each endpoint (GMTs and seroconversion rates).

- **Immunogenicity Analysis Populations**
  - **Per Protocol Population**
    - As in Protocol 016, the PPI population included all subjects without protocol violations who received all 3 vaccinations within acceptable day ranges, who were seronegative at Day 1 to the respective HPV type(s), and who had a valid serology result within an acceptable day range following the third injection.
  - **All Type-Specific HPV-Naïve Subjects With Serology Data Population**
    - The all type-specific HPV-naïve subjects with serology data population included all subjects who were seronegative to the appropriate vaccine component(s) at Day 1, received all 3 vaccinations, and had a valid Month 7 serology result. This population included general protocol violators and considered incorrectly randomized subjects in the analysis according to the vaccination group to which they were randomized.

- **Safety Objectives**
  - In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, VRC-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever. Risk differences were calculated for AEs comparing the vaccine and placebo groups across all vaccination visits with respect to all AEs with ≥ 1% incidences. p-values were computed for VRC elicited adverse events only
  - Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits.
  - Risk differences and associated exact 95% confidence intervals were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with 1% incidence in either vaccination group.
  - Elevated temperatures (≥ 37.8° C [≥ 100° F] oral or oral equivalent) within 5 days following each vaccination were summarized in a similar manner.
- **Safety Analysis Population:** All subjects who received at least one injection and had follow-up data were included in the safety summary.

Changes in Protocol and Statistical Analysis: Three protocol amendments and one informational amendment were submitted to the IND and reviewed prior to unblinding. Changes in statistical analysis did not impact on the primary safety and immunogenicity results. **See Appendix 18 for details.**

Results
Populations Enrolled/Analyzed

TABLE 212
Protocol 018: Subject Disposition by Vaccination Group

	Quadrivalent Vaccine	Non-Alum Placebo	Total
	n/%	n/%	n/%
Subjects screened but not enrolled (failure to meet I/E criteria)			20
Randomized	1184	597	1781
Vaccinated at:			
Dose 1	1179 (99.6%)	596 (99.8%)	1775 (99.7%)
Dose 2	1149 (97.0%)	573 (96.0%)	1722 (96.7%)
Dose 3	1123 (94.8%)	562 (94.1%)	1685 (94.6%)
Vacination Period (Day 1 through Month 7)			
Entered	1179	596	1775
Completed	1120 (95.0%	560 (94.0%)	1680 (94.6%)
Continuing	1(0.1%)	0	1 (0.1%)
Discontinued	58 (4.9%)	36 (6.0%)	94 (5.3%)
With long term follow-up	7 (0.6%)	4 (0.7%)	11 (0.6%)
Clinical AE	2 (0.2%)	0 (0.0%)	2 (0.1%)
Other reasons	5 (0.4%)	4 (0.7%)	9 (0.5%)
Without long term follow-up	51 (4.3%)	32 (5.4%)	83 (4.7%)
Clinical AE	1 (0.1%)	0 (0.0%)	1 (0.1%)
Lost to f/u	18 (1.5%)*	7 (1.2%)	25 (1.4%)*
Moved	3 (0.3%)*	1 (0.2%)	4 (0.3%)*
Other reasons	1 (0.1%)	2 (0.3%)	3 (0.2%)
Parent withdrew consent	9 (0.8%)	8 (1.3%)	17 (1.0%)
Withdrew consent	19 (1.6%)	14 (2.3%)	33 (1.9%)

*One subject was added to lost to f/u in Gardasil group and 1 deleted from moved in Gardasil group in the Month 12 Safety Report.
Source: Table 6-1, CSR 018, p. 93 and Table 4-1, M12 Safety Report 018, p. 12-13

- The CSR covered the period through Month 7. A separate report was submitted for preliminary Month 12 safety data and another separate report is to be submitted through Month 18.

TABLE 213
Protocol 018: Subject Disposition for Females (9-15 years of age) by Vaccination Group

	Quadrivalent Vaccine	Non-Alum Placebo	Total
	n/%	n/%	n/%
Randomized	617	322	939
Vaccinated at:			
Dose 1	615 (99.7%)	321 (99.7%)	936 (99.7%)
Dose 2	603 (97.7%)	306 (95.0%)	909 (96.8%)
Dose 3	587 (95.1%)	301 (93.5%)	888 (94.6%)
Vacination Period (Day 1 through Month 7)			
Entered	615	321	936
Completed	587 (95.4%)	301 (93.8%)	888 (94.9%)
Continuing	0	0	0
Discontinued	28 (4.6%)	20 (6.2%)	48 (5.1%)
With long term follow-up	4 (0.7%)	1 (0.3%)	5 (0.5%)
Clinical AE	1 (0.2%)	0 (0.0%)	1 (0.1%)
Other reasons	3 (0.5%)	1 (0.3%)	4 (0.4%)
Without long term follow-up	24 (3.9%)	19 (5.9%)	43 (4.6%)
Clinical AE	0	0 (0.0%)	0 (0.0%)
Lost to f/u	9 (1.5%)	4 (1.2%)	13 (1.4%)
Moved	2 (0.3%)	1 (0.3%)	3(0.3%)
Other reasons	1 (0.2%)	1 (0.3%)	2 (0.2%)
Parent withdrew consent	2 (0.3%)	7 (2.2%)	9 (1.0%)
Withdrew consent	10 (1.6%)	6 (1.9%)	16 (1.7%)

Source: From Table 6-2, CSR 018v1, p. 94

- A comparable proportion of study subjects completed the study in each group, and very few discontinued due to an AE. (The same can be said for the boys).
- Findings are similar when the groups are separated by age strata (9-12 years and 13-15 years).
- Overall, there were 696 subjects randomized, and 692 vaccinated with at least one dose of vaccine for the 9-12 year old age group, and 488 randomized and 487 vaccinated in the 13-15 year old age group. (Source: Table 11-2, CSR 018v1, p. 188, not shown here)

TABLE 214
Protocol 018: Subject Disposition for Males
(aged 9-15 years of age) by Vaccination Group

	Quadrivalent Vaccine	Non-Alum Placebo	Total
	n/%	n/%	n/%
Randomized	567	275	842
Vaccinated at:			
Dose 1	564 (99.5%)	275 (100.0%)	839 (99.6%)
Dose 2	546 (96.3%)	267 (97.1%)	813 (96.6%)
Dose 3	536 (94.5%)	261 (94.9%)	797 (94.7%)
Vacination Period (Day 1 through Month 7)			
Entered	564	275	839
Completed	533 (94.5%)	259 (94.2%)	792 (94.4%)
Continuing	1 (0.2%)	0 (0.0%)	1 (0.1%)
Discontinued	30 (5.3%)	16 (5.8%)	46 (5.5%)
With long term follow-up	3 (0.5%)	3 (1.1%)	6 (0.7%)
Clinical AE	1 (0.2%)	0 (0.0%)	1 (0.1%)
Other reasons	2 (0.4%)	3 (1.1%)	5 (0.6%)
Without long term follow-up	27 (4.8%)	13 (4.7%)	40 (4.8%)
Clinical AE	1 (0.2%)	0 (0.0%)	1 (0.1%)
Lost to f/u	*9 (1.4%)	3 (1.1%)	11 (1.3%)
Moved	2 (0.4%)	0 (0.0%)	2 (0.2%)
Other reasons	0 (0.0%)	1 (0.4%)	1 (0.1%)
Parent withdrew consent	7 (1.2%)	1 (0.4%)	8 (1.0%)
Withdrew consent	9 (1.6%)	8 (2.9%)	17 (2.0%)

Continuing subjects: One subject did not complete the Month 7 visit by the cutoff date, but did not withdraw from the study.
Source: From Table 6-2, CSR 018v1, p. 94 and Month 12 Safety Update (*one additional subject in Gardasil group was lost to follow-up)

Immunogenicity Population Analyzed

- The most common reason for exclusion among girls and boys for exclusion from the PPI population were Month 7 serology samples obtained outside of the acceptable day ranges and incomplete vaccination series. Failure to receive the 3 vaccines within appropriate day ranges was also among the more common reasons to be excluded from the PPI population (moreso for girls than for boys). This is shown in the table below.

TABLE 215
Protocol 018: Summary of Exclusions from Per-Protocol Population by Gender in the Quadrivalent Vaccine Group only

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine		
	Boys (N=567) n	Girls (N=617) n	Total (N=1184) n
Subjects who received at least 1 injection	564	615	1179
Subjects excluded from Per-Protocol Population			
HPV 6/11	93	114	207
HPV 16	93	113	206
HPV 18	90	112	202
Subjects included in Per-Protocol Population			
HPV 6/11	471	501	972
HPV 16	471	502	973
HPV 18	474	503	977
Reason for exclusion:			
General protocol violation	57	72	129
Vaccine storage temperature out of range	11	10	21
Incomplete vaccination series	28	28	56
Incorrect dose or incorrect clinical material	3	0	3
Vaccination 2 or 3 out of acceptable day range	11	23	34
Received non-study vaccination†	4	7	11
Received immunosuppressives, IgG, or blood products	3	6	9
Engaged in sexual intercourse	1	2	3
Missing Day 1 serology sample/results	9	13	22
Missing Month 7 serology sample/results‡	5	5	10
Month 7 serology sample out of acceptable day range‡	28	30	58
Day 1 seropositive to HPV 6 or 11§	4	5	9
Day 1 seropositive to HPV 16§	4	4	8
Day 1 seropositive to HPV 18§	1	2	3

† Includes (1) any live vaccine received within 21 days prior to or 14 days following study vaccine, or (2) any inactivated or recombinant vaccine received within 14 days of study vaccine.
‡ Among subjects who received all 3 injections.
§ Applies to the population for the relevant HPV type(s) only. Seropositive is defined as an anti-HPV Luminex antibody level ≥ 20, 16, 20, or 24 milli Merck Units/mL for HPV Types 6, 11, 16 or 18, respectively.
Subjects are counted once in each applicable exclusion category. A subject may appear in more than one category.
N = Number of subjects in the respective demographic cohort.
n = Number of subjects with the indicated characteristic.
HPV = Human papillomavirus; VLP = Virus-like particles.

Source: Table 6-3, CSR 018v1, p. 98

TABLE 216
Protocol 018: Summary of Exclusions from PPI Population
By Gender in the Placebo Group Only

	Non-Alum Placebo		
	Boys (N=275) n	Girls (N=322) n	Total (N=597) n
Subjects who received at least 1 injection	275	321	596
Subjects excluded from Per-Protocol Population			
HPV 6/11	52	66	118
HPV 16	52	67	119
HPV 18	50	63	113
Subjects included in Per-Protocol Population			
HPV 6/11	223	255	478
HPV 16	223	254	477
HPV 18	225	258	483
Reason for exclusion:			
General protocol violation	36	41	77
Vaccine storage temperature out of range	7	5	12
Incomplete vaccination series	14	20	34
Incorrect dose or incorrect clinical material	2	1	3
Vaccination 2 or 3 out of acceptable day range	8	10	18
Received non-study vaccination†	2	4	6
Received immunosuppressives, IgG, or blood products	5	2	7
Missing Day 1 serology sample/results	5	7	12
Missing Month 7 serology sample/results‡	2	1	3
Day 1 serology sample out of acceptable day range	1	0	1
Month 7 serology sample out of acceptable day range‡	10	23	33
Day 1 seropositive to HPV 6 or 11§	2	6	8
Day 1 seropositive to HPV 16§	2	8	10
Day 1 seropositive to HPV 18§	0	2	2

† Includes (1) any live vaccine received within 21 days prior to or 14 days following study vaccine, or (2) any inactivated or recombinant vaccine received within 14 days of study vaccine.
‡ Among subjects who received all 3 injections.
§ Applies to the population for the relevant HPV type(s) only. Seropositive is defined as an anti-HPV Luminex antibody level ≥ 20, 16, 20, or 24 milli Merck Units/mL for HPV Types 6, 11, 16, or 18, respectively.
Subjects are counted once in each applicable exclusion category. A subject may appear in more than one category.
N = Number of subjects in the respective demographic cohort who were randomized to the placebo group.
n = Number of subjects in the respective category.
HPV = Human papillomavirus; VLP = Virus-like particles.

Source: Table 11-3, CSR 018v1, p. 194

Demographics

- There were 47 study sites in 10 countries in the 4 geographic regions. At each site, there is an approximate 2:1 vaccinee: placebo ratio.
- The overall baseline characteristics are presented in Table 217 below. The baseline characteristics are also broken down by age strata (9-12 years of age and 13-15 years of age) and by gender.
- The weight of the 13-15 year old subjects is observationally higher than the children who are 9-12 years of age, although the BMIs are not as far apart.

TABLE 217
Protocol 018: Summary of Subject Characteristics by Demographic Cohort

	Quadrivalent Vaccine	Non-Alum Placebo	Total
Gender			
Female	617 (52.1%)	322 (53.9%)	939 (52.7%)
Male	567 (47.9%)	275 (46.1%)	842 (47.3%)
Age (years)			
Mean	11.9	11.8	11.9
Range	9-16	9-15	9-16
Weight (kg)			
Mean	48.8	49.2	48.9
Range	19-130	22-139	19-139
BMI			
Mean	20.4	20.7	20.5
Range	9-46	13-51	9-51
Race			
Asian	149 (12.6%)	70 (11.7%)	219 (12.3%)
Black	50 (4.2%)	21 (3.5%)	71 (4.0%)
Hispanic American	260 (22.0%)	130 (21.8)	390 (21.9%)
Native American	0 (0.0%)	1 (0.2%)	1 (0.1%)
White	716 (60.5%)	369 (61.8%)	1085 (60.9%)
Other	9 (0.8%)	6 (1.0%)	15 (0.8%)

Source: Table 6-5, CSR 018v1, p. 103-4

- The proportion of subjects in each treatment group in each region are comparable. See Table 218 below.

TABLE 218
Protocol 018: Subjects Enrolled by Region

Region	**Quadrivalent HPV Vaccine N=1184**	**Non-Alum Placebo N=597**	**Total N=1781**
Asia-Pacific	144 (12.2%)	68 (11.4%)	212 (11.9%)
Europe	342 (28.9%)	170 (28.5%)	512 (28.7%)
Latin America	210 (17.7%)	107 (17.9%)	317 (17.8%)
North America	488 (41.2%)	252 (42.2%)	740 (41.5%)

From: Table 6-5, CSR 018v1, p. 103-4

- A summary of subject characteristics by gender is provided in Table 219 below. The subject characteristics are similar for girls and boys, and for vaccine recipients and placebo recipients.

TABLE 219
Protocol 018: Summary of Subject Characteristics by Gender Within Vaccination Group

	Quadrivalent Vaccine		Non-Alum Placebo	
	Boys N=567	Girls N=617	Boys N=275	Girls N=322
Age (years)				
Mean	12	11.9	11.8	11.8
Range	9-16	9-15	9-15	9-15
Weight (kg)				
Mean	49.4	48.2	48.6	49.7
Range	22-130	19-122	22-103	23-139
BMI				
Mean	20.2	20.5	20.3	21.1
Range	12-41	9-46	14-39	13-51
Race				
Asian	67 (11.8%)	82 (13.3%)	37 (13.5%)	33 (10.2%)
Black	26 (4.6%)	24 (3.9%)	11 (4.0%)	10 (3.1%)
Hispanic American	123 (21.7%)	137 (22.2%)	61 (22.2%)	69 (21.4%)
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
White	346 (61.0%)	370 (60.0%)	162 (58.9%)	207 (64.3%)
Other	5 (0.9%)	4 (0.6%)	4 (1.5%)	2 90.6%)
Region				
Asia-Pacific	63 (11.1%)	81 (13.1%)	36 (13.1%)	32 (9.9%)
Europe	156 (27.5%)	186 (30.1%)	72 (26.2%)	98 (30.4%)
Latin America	102 (18.0%)	108 (17.5%)	45 (16.4%)	62 (19.3%)
US and Canada	246 (43.4%)	242 (39.2%)	122 (44.4%)	130 (40.4%)

Source: Table 6-6, CSR 018v1, p. 105

- A summary of subject characteristics is also provided by age strata. The BMI and weights are higher in the older age stratum (13-15 years) as compared to the younger age stratum (9-12 years).

TABLE 220
Protocol 018: Summary of Subject Characteristics by Age Group Within Vaccination Group

	Quadrivalent Vaccine		Non-Alum Placebo	
	9-12 years of age N=696	13-15 years of age N=488	9-12 years of age N=372	13-15 years of age N=225
Gender				
Female	364 (52.3%)	253 (51.8%)	199 (53.5%)	123 (54.7%)
Male	332 (47.7%)	235 (48.2%)	173 (46.5%)	102 (45,3%)
Weight (kg)				
Mean	42.1	58.4	43.6	58.5
Range	19-93	28-130	22-94	34-139
BMI				
Mean	19.4	21.8	20.0	22.0
Range	12-41	9-46	13-40	15-51
Race				
Asian	97 (13.9%)	52 (10.7%)	46 (12.4%)	24 (10.7%)
Black	28 (4.0%)	22 (4.5%)	13 (3.5%)	8 (3.6%)
Hispanic American	159 (22.8%)	101 (20.7%)	88 (23.7%)	42 (18.7%)
Native American	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
White	407 (58.5%)	309 (63.3%)	220 (59.1%)	149 (66.2%)
Other	5 (0.7%)	4 (0.8%)	1 (0.4%)	1 (0.4%)
Region				
Asia-Pacific	94 (13.5%)	50 (10.2%)	46 (12.4%)	22 (9.8%)
Europe	214 (30.7%)	128 (26.2%)	109 (29.3%)	61 (27.1%)
Latin America	127 (18.2%)	83 (17.0%)	71 (19.1%)	36 (16.0%)
US and Canada	261 (37.5%)	227 (46.5%)	146 (39.2%)	106 (47.1%)

Source: Table 6-7, CSR 018v1, p. 106

HPV 6, 11, 16, 18 Serostatus Day 1

1.8% of the girls and 1.6% boys were seropositive to a vaccine HPV type. (Seropositive is defined as anti-HPV serum cLIA levels 20, 16, 20, 24 mMU/mL for HPV Types 6, 11, 16, and 18, respectively) Source: Table 6-8, CSR 018v1, p. 108, not shown here

- A somewhat higher proportion of placebo recipients were seropositive to a vaccine HPV type (3.1%) compared to 1.7% of the vaccinees. (Source: Table 11-4, CSR 018v1, p. 195)

The treatment groups were comparable with regards to prior and concomitant medications and vaccinations, medical history and treatment compliance.

Immunogenicity Results

- The GMTs and seroconversion rates (seroconversion rate = proportion achieving anti-HPV serum cLIA levels $\geq$ 20, 16, 20, 24 mMU/mL for HPV Types 6, 11, 16, and 18, respectively) of girls and boys who received vaccine are provided in Tables 221 and 222. The boys were noted to have higher GMTs as compared to girls, although seroconversion rates were nearly identical.

TABLE 221
Protocol 018: Summary of HPV GMTs by Gender Among Subjects who Received the Quadrivalent HPV Vaccine (Per Protocol Immunogenicity Population)

Assay	Time Point	Boys N=564		Girls N=615	
		n	GMT (mMU/mL) 95% CI	n	GMT (mMU/mL) 95% CI
Anti-HPV 6	Month 7	471	967.6 (884.8, 1058.1)	501	884.3 (813.3, 961.6)
Anti-HPV 11	Month 7	471	1383.5 (1263.8, 1514.4)	501	1336.3 (1225.4, 1457.2)
Anti-HPV 16	Month 7	471	6193.0 (5540.0, 6923.0)	502	5006.9 (4500.9, 5569.8)
Anti-HPV 18	Month 7	474	1474.5 (1317.9, 1649.8)	503	1127.8 (1017.0, 1250.6)

Source: Table 7-1, CSR 018v1, p. 121

TABLE 222
Protocol 018: Summary of Month 7 Seroconversion Rates by Gender among Subjects who Received the Quadrivalent Vaccine (Per Protocol Immunogenicity Population)

Assay	Time Point	Boys N=564		Girls N=615	
		n	Seroconversion 95% CI	n	Seroconversion 95% CI
Anti-HPV 6	Month 7	471	99.8% (98.8, 100%)	501	99.8% (98.9, 100%)
Anti-HPV 11	Month 7	471	99.8% (98.8, 100%)	501	99.8% (98.9, 100%)
Anti-HPV 16	Month 7	471	99.6% (98.5, 99.9%)	502	99.8% (98.9, 100%)
Anti-HPV 18	Month 7	474	99.8% (98.8, 100%)	503	99.6% (98.6, 100%)

Seroconversion is change in serostatus from seronegative to seropositive. Seropositive for HPV 6, 11, 16, and 18 cLIAs are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Table 702, CSR 018v1, p. 122

- Overall, 4 subjects failed to seroconvert at Month 7 to a vaccine HPV type.
  - vaccinees did not seroconvert to any vaccine HPV type. (It is possible that the labels for these 2 vaccinees at two sites were switched with those for 2 subjects at the same sites who received the placebo and had very high anti-HPV antibody levels [vaccine types]). The 2 placebo recipients had very high antibody levels to all 4 vaccine HPV types. (Source: Table 11-11, CSR 018v1, p. 237, not shown here)
  - 2 vaccinees did not seroconvert to one of the vaccine HPV types (a 10 year old male and a 15 year old female). (Source: Table 11-12, CSR 018v1, p. 238, not shown here)
- The GMTs and seroconversion rates for the all HPV naïve with serology population were similar to those seen in the PPI population. (Source: Tables 11-13, 11-14, CSR 018v1, p. 239-40, not shown here)

- **Comparison of immune responses in girls and boys**
  - **GMTs:** The statistical criteria for non-inferiority was met. The LB of the 95% CI for the fold-difference in GMTs (boys/girls) was > 0.5 (it excluded a decrease of 2-fold or more) for each vaccine HPV type. See Table 223 below.

TABLE 223
Protocol 018: Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA GMTs Comparing 9-15 year old Males to 9-15 year old Females (PPI Population)

Assay	Comparison Group: Boys Comparison Group A N=564		Comparison Group: Girls Comparison Group B N=6		Estimated Fold Difference Group A/Group B (95% CI)	p-value for non-inferiority
	N	**Estimated GMT (mmU/mL)**	N	**Estimated GMT (mmU/mL)**		
Anti-HPV 6	471	**1003.7**	501	**807.7**	**1.24** (1.03, 1.49)	< 0.001
Anti-HPV 11	471	**1333.8**	501	**1184.7**	**1.13** (0.93, 1.36)	< 0.001
Anti-HPV 16	471	**6345.1**	502	**4513.0**	**1.41** (1.11, 1.78)	< 0.001
Anti-HPV 18	474	**1577.5**	503	**1073.8**	**1.47** (1.17, 1.85)	< 0.001

Source: Table 7-3, CSR 018v1, p. 125

  - **Seroconversion:** The statistical criteria for non-inferiority was met: the LB of the 95% CI for the difference in proportions between the two groups (boys – girls) was > 5.0 (i.e., it excluded a decrease of 5% points or more) for each vaccine HPV type. See Table 224 below.

TABLE 224
Protocol 018: Statistical Analysis of Non-Inferiority of Month 7 Anti-HPV Seroconversion Rates Comparing Boys with Girls Among Subjects who Received Quadrivalent HPV Vaccine (PPI Population)

	Boys N=564		Girls N=615		Estimated Percentage Point Difference Boys minus Girls 95% CI	p-value for non-inferiority
Anti-HPV Response	n	Estimated Response (%)	n	Estimated Response (%)		
HPV 6 cLIA ≥ 20 mMU/mL	471	99.8%	501	99.8%	-0.0 (-1.1, 0.9)	<0.001
HPV 11 cLIA ≥ 16 mMU/mL	471	99.8%	501	99.8%	-0.0 (-1.1, 0.9)	<0.001
HPV 16 cLIA ≥ 20 mMU/mL	471	99.6%	502	99.8%	-0.2 (-1.4, 0.7)	<0.001
HPV 18 cLIA ≥ 24 mMU/mL	474	99.8%	503	99.6%	0.2 (-0.8, 1.2)	<0.001

Source: Table 7-4, CSR 018, p. 126

- Analyses comparing GMTs and serconversion rates between girls and boys who received vaccine were performed in the all HPV naïve with serology population, and these results were similar to the above analyses in the PPI population. (Source: Tables 11-15, 11-16, CSR 018v1, p. 241-2, not shown here)

Immunogenicity Evaluation by Vaccination Group

A summary of immune responses by GMTs and seroconversion rates are also presented for all vaccine recipients compared to placebo recipients. These are shown in Tables 225 and 226 below.

TABLE 225
Protocol 018: Summary of HPV GMTs Among Subjects by Treatment Group (Per Protocol Immunogenicity Population)

Assay	Time Point	HPV Vaccine N=1179		Non-Alum Placebo N=596	
		n	GMT 95% CI	n	GMT 95% CI
Anti-HPV 6	Month 7	972	923.7 (869.0, 982.0)	478	< 8 (< 8, < 8)
Anti-HPV 11	Month 7	972	1359.0 (1276.4, 1446.6)	478	< 8 (< 8, < 8)
Anti-HPV 16	Month 7	973	5549.6 (5137.5, 5994.9)	477	< 12 (< 12, < 12)
Anti-HPV 18	Month 7	977	1284.4 (1189.8, 1386.6)	483	< 8 (< 8, < 8)

Source: Table 7-5, CSR 018v1, p. 130

TABLE 226
Protocol 018: Summary of Month 7 Seroconversion Rates by Treatment groups (Per Protocol Immunogenicity Population)

Assay	Time Point	HPV Vaccine N=1179		Non-Alum Placebo N=596	
		n	Seroconversion 95% CI	n	Seroconversion 95% CI
Anti-HPV 6	Month 7	972	99.8% (99.3, 100%)	478	1.9% (0.9, 3.5%)
Anti-HPV 11	Month 7	972	99.8% (99.3, 100%)	478	2.3% (1.2, 4.1%)
Anti-HPV 16	Month 7	973	99.7% (99.1, 99.9%)	477	2.9% (1.6, 4.9%)
Anti-HPV 18	Month 7	977	99.7% (99.1, 99.9%)	483	1.2% (0.5, 2.7%)

Seroconversion = change in serostatus from seronegative to seropositive. A subject is considered seropositive for HPV 6, 11, 16, and 18 if the cLIA titers are $\geq$ 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Table 7-6, CSR 018v1, p. 131

- Overall, 18 subjects who were in the PPI population and who received placebo were found to be seropositive to at least one vaccine HPV type at Month 7. The sponsor postulates that the reasons for some placebo recipients becoming positive include

issues of assay specificity, sample mislabeling, or failure to identify receipt of incorrect study material due to third party blinding. (Source: Table 11-22, CSR 018v1, p. 250 and narratives in Section II.11.2)

Reviewer's Comment: There were 4 placebo recipients who may have incorrectly received vaccine (based on the levels of antibodies noted). 7 of the other subjects became seropositive to only one vaccine HPV type potentially were exposed to natural HPV infection with one of the vaccine HPV type (HPV 16). 7 others became seropositive to 2 or 3 of the vaccine HPV types.

Immunogenicity Evaluation by Age Group Among Vaccinees

- The GMTs and seroconversion rates in subjects 9-12 years of age with subjects 13-15 years of age were also compared. The younger subjects had higher GMTs for all vaccine HPV types as compared to the older subjects. Seroconversion rates were almost identical in both age groups. See Tables 227 and 228 below.

TABLE 227
Protocol 018: Summary of HPV GMTs by Age Group Among Subjects who Received the Quadrivalent HPV Vaccine (Per Protocol Immunogenicity Population)

Assay	Time Point	9-12 Year s of age		13-15 years of age	
		n	GMT 95% CI	n	GMT 95% CI
Anti-HPV 6	Month 7	572	1058.2 (980.2, 1142.4)	400	760.6 (689.9, 838.6)
Anti-HPV 11	Month 7	572	1594.6 (1477.1, 1721.5)	400	1081.1 (976.9, 1196.5)
Anti-HPV 16	Month 7	574	6498.6 (5895.9, 7162.8)	399	4422.3 (3911.0, 5000.3)
Anti-HPV 18	Month 7	576	1558.9 (1417.2, 1714.7)	401	972.5 (860.9, 1098.7)

Source: Table 7-7, CSR 018v1, p. 132

TABLE 228
Protocol 018: Summary of Month 7 Seroconversion Rates by Age Group Among Subjects who Received the Quadrivalent Vaccine (Per Protocol Immunogenicity Population)

Assay	Time Point	9-12 years of age		13-15 years of age	
		n	GMT 95% CI	n	GMT 95% CI
Anti-HPV 6	Month 7	572	99.8% (99.0, 100%)	400	99.8% (98.6, 100%)
Anti-HPV 11	Month 7	572	99.8% (99.0, 100%)	400	99.8% (98.6, 100%)
Anti-HPV 16	Month 7	574	99.7% (98.7, 100%)	398	99.7% (98.6, 100%)
Anti-HPV 18	Month 7	576	99.8% (99.0, 100%)	401	99.5% (98.2, 99.9%)

Seroconversion = change in serostatus from seronegative to seropositive. A subject is considered seropositive for HPV 6, 11, 16, and 18 if the cLIA titers are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively.
Source: Table 7-8, CSR 018v1, p. 133

Immunogenicity Evaluation in Initially Baseline Seropositive Subjects

- There were very few subjects who were initially seropositive (19, and 18 [9 girls and 9 boys] overall had serology at Month 7).
  - In girls who were initially seropositive: HPV 6 (4): The GMTs in those who were initially seropositive were higher than the GMT point estimate in the PPI population; HPV 16 (3): GMTs in those who were initially seropositive were lower than the GMT point estimate in the PPI population; HPV 18 (2): One GMT was higher and one GMT was lower in those who were initially seropositive than the GMT point estimate in PPI population. (Source: Table 11-23, CSR 018v1, p. 251, not shown here)

Safety Results

- Overall, a higher proportion of vaccine recipients reported one or more AEs compared with placebo recipients. This was largely due to a higher proportion of vaccine recipients with injection site AEs compared to placebo recipients. The proportion of subjects with systemic AEs was comparable in the 2 groups.
- Overall, **5 SAEs occurred within the 14 days after any vaccination**. All of these occurred after receipt of the vaccine and none after placebo. (These are detailed later in the review).
- 2 subjects **discontinued due to an AE (**both in the vaccine group). (These are detailed later in the review).
- The AEs postdose 1, 2, and 3 were generally consistent with those described for the overall clinical AE summary. Higher proportions of subjects in the vaccine and placebo reported AEs (overall, injection site, and systemic AE) following dose 1 compared with postdoses 2 and 3. (Source: Tables 11-26, 11-27, 11-28, CSR 018v1, p. 254-6, not shown here)
- The AEs in the 9-12 year olds and 13-15 year olds were generally comparable to the overall AE summary. 4/5 of the SAEs occurred in the 13-15 year olds.

TABLE 229
Protocol 018: Clinical Adverse Experience
Summary Days 1-15 Postvaccination – Protocol 018 (Overall)

	HPV vaccine group N=1179	Placebo group N=594
Subjects with follow-up	1165	584
N (%) with 1+ AE	**963 (82.7%)**	**392 (67.1%)**
N (%) with IS AE	**877 (75.3%)**	**292 (50.0%)**
N (%) with systemic AE	541 (46.4%)	260 (44.5%)
N (%) with SAE	**5 (0.4%)**	**0 (0.0%)**
Deaths	0	0
D/C due to AE	3 (0.3%)	0(0.0%)
D/C due to SAE	1 (0.1%)	0 (0.0%)

Source: From Table 8-1, CSR 018v1, p. 140

- There was a statistically higher proportion of subjects in the vaccine group with an AE as compared to the saline placebo group. (See Table 230 below).

TABLE 230
Protocol 018: Comparison of Overall Rate of AEs
(Days 1 – 15 after any vaccination)

	Gardasil N=1179	Placebo N=594	Risk Difference Gardasil – Placebo	95% CI
Subjects with follow-up	1165	584		
Subjects with one or more AE	**963 (82.7%)**	**392 (67.1%)**	**15.5%**	**(11.2, 20.0)**

Source: From Table in Protocol 018, Question 1, Amendment 0017, efficacy information amendment 3/30/06.

- In each vaccination group, a higher proportion of girls reported an AE compared with the boys. (See Table 231 below).

TABLE 231
Protocol 018: Clinical Adverse Experience Summary
Days 1-15 Postvaccination by Gender

	HPV Vaccine		Non-alum placebo	
	Boys 9-15 years N=564	Girls 9-15 years N=615	Boys 9-15 years N=274	Girls 9-15 years N=320
Subjects with follow-up	557	608	269	315
N (%) with 1+ AE	441 (79.2%)	**522 (85.9%)**	173 (64.3%)	**219 (69.5%)**
N (%) with IS AE	388 (69.7%)	**489 (80.4%)**	130 (48.3%)	**162 (51.4%)**
N (%) with systemic AE	247 (44.3%)	**294 (48.4%)**	110 (40.9%)	**150 (47.6%)**
N (%) with SAE	**3 (0.5%)**	**2 (0.3%)**	**0 (0.0%)**	**0 (0.0%)**
Deaths	0	0	0	0
D/C due to AE	**2 (0.4%)**	**1 (0.2%)**	0	0
D/C due to SAE	**1 (0.2%)**	0	**0**	0

Source: From Table 11-24, CSR 018v1, p. 252

- The overall proportions of subjects with an AE were similar when comparing the 9-12 year old subjects with the 13-15 year old subjects who received vaccine. The 13-15 year old vaccine recipients had a lower overall proportion of subjects with an injection site AE as compared to 9-12 year old vaccine recipients (with the same pattern noted for placebo). The 13-15 year old vaccine recipients had a slightly higher proportion of subjects with systemic AEs as compared to the 9-12 year old vaccine recipients. A similar proportion of 9-12 year old vaccine recipients had systemic AEs as compared to 9-12 year old placebo recipients. (See Table 232 below).

TABLE 232
Protocol 018 - Clinical Adverse Experience Summary
Days 1-15 Postvaccination by Age

	HPV Vaccine		Non-alum placebo	
	9-12 years of age N=692	13-15 years of age N=487	9-12 years of age N=370	13-15 years of age N=224
Subjects with follow-up	683	482	364	220
N (%) with 1+ AE	567 (83.0%)	396 (82.2%)	244 (67.0%)	148 (67.3%)
N (%) with IS AE	528 (77.3%)	349 (72.4%)	187 (51.4%)	105 (47.7%)
N (%) with systemic AE	301 (44.1%)	240 (49.8%)	160 (44.0%)	100 (45.5%)
N (%) with SAE	1 (0.1%)	4 (0.8%)	0	0
Deaths	0	0	0	0
D/C due to AE	1 (0.1%)	2 (0.4%)	0	0
D/C due to SAE	0	1 (0.2%)	0	0

Source: From Table 11-25, CSR 018v1, p. 253

Safety and Baseline Serostatus

- For subjects who were initially seropositive (36 subjects) who received at least one vaccination:
  - The proportions of subjects with one or more AE were comparable between the 2 groups.
  - A higher proportion of subjects in the vaccine group had injection site AEs compared to those in the placebo group.
  - The overall incidences of AEs, and the incidences of injection site AEs appeared somewhat lower in those who were initially seropositive as compared to those who were initially seronegative. However, the numbers are small.

  (Source: Tables 11-30, 11-31, CSR 018v1, p. 258-9, not shown here)

Intensities of AEs

- The proportions of subjects reporting a moderate or severe injection site AE (of all subjects with follow-up data) were higher in the quadrivalent vaccine group (32.5% for moderate, and 10.6% for severe) as compared to the non-alum placebo group (23.6% for moderate and 6.8% for severe).
- Among all reported AEs, the frequency of intensity ratings appeared comparable between the 2 vaccination groups.
- There were 3 AEs reported per vaccine recipient, and 2 AEs reported per placebo recipient. (Source: Tables 8-2, and 8-3, CSR 018v1, p. 143, not shown here)

Injection Site AEs

- In both vaccination groups, the most common injection site AE was pain in the 5 days after any vaccination. (See Table 233 below).

TABLE 233
Protocol 018: Number (%) of subjects with Injection Site AEs
Days 1-5 after any Vaccination Visit

	Quadrivalent HPV Vaccine Recipients N=1179	Non-Alum Placebo Recipients N=594
Subjects with follow-up	1165	584
Number (%) with IS AE	877 (75.3%)	289 (49.5%)
Injection site pain	853 (73.2%)	265 (45.4%)
Injection site swelling	241 (20.7%)	45 (7.7%)
Injection site erythema	237 (20.3%)	77 (13.2%)

Source: From Table 8-4, p. 147 and Table 11-32, p. 260, CSR 018v1

- Significantly higher proportions of vaccine recipients reported injection site erythema, pain and swelling as compared to placebo recipients. Risk differences were compared. (See Table 234 below.)

TABLE 234
Protocol 018: Comparison of Vacination Groups with Respect to the Number (%) of Subjects who Reported Specific Injection Site AEs Days 1-5 after any Vaccination

	Quadrivalent HPV Vaccine Recipients N=1179	Non-Alum Placebo Recipients N=594	Risk Difference and 95% CI	p-value
Subjects with follow-up	1165	584		
Number (%) with IS AE	**877 (75.3%)**	**289 (49.5%)**	**25.8 % (21.0, 30.5%)**	
Injection site pain	**853 (73.2%)**	**265 (45.4%)**	**27.8 % (23.0, 32.6)**	**< 0.001**
Injection site swelling	**241 (20.7%)**	**45 (7.7%)**	**13.0 % (9.7, 16.1%)**	**< 0.001**
Injection site erythema	**237 (20.3%)**	**77 (13.2%)**	**7.3% (3.4, 10.7%)**	**< 0.001**

Source: From Table 8-5, CSR 018v1, p. 148

- The proportions of subjects with njection site AEs within each gender group were generally comparable to those observed in the study overall. In the vaccine group, the proportion of girls who reported one or more injection site AE (80.4%) was higher than the proportion of boys with one or more injection site AE (69.7%). (See Table 235 below).

TABLE 235
Protocol 018: Number (%) of Subjects with Injection Site AEs by Gender Within Each Vaccination Group (Days 1-5 After any Vaccination Visit)

	Quadrivalent HPV Vaccine Recipients		**Non-Alum Placebo Recipients**	
	Boys 9-15 years N=564	**Girls 9-15 years N=615**	Boys 9-15 years N=274	**Girls 9-15 years N=320**
Subjects with follow-up	557	**608**	269	**315**
Number (%) with IS AE	388 (69.7%)	**489 (80.4%)**	128 (47.6%)	**161 (51.1%)**
Injection site pain	375 (67.3%)	**478 (78.6%)**	112 (41.6%)	**153 (48.6%)**
Injection site swelling	91 (16.3%)	**150 (24.7%)**	22 (8.2%)	**23 (7.3%)**
Injection site erythema	103 (18.5%)	**134 (22.0%)**	39 (14.5%)	**38 (12.1%)**

Source: From Table 11-33, CSR 018v1, p. 261-2

- The proportion of subjects with specific injection site AEs within each age stratum are provided in Table 236 below. Injection site pain, swelling and erythema were reported in a higher proportion of vaccine recipients 9-12 years of age as compared to vaccine recipients 13-15 years of age.

TABLE 236
Protocol 018: Number (%) of Subjects with Injection Site AEs by Age Group Within Each Vaccination Group (Days 1-5 After any Vaccination Visit)

	Quadrivalent HPV Vaccine Recipients		**Non-Alum Placebo Recipients**	
	Subjects 9-12 years of age (N=692)	Subjects 13-15 years of age (N=487)	Subjects 9-12 years of age (N=370)	Subjects 13-15 years of age (N=224)
Subjects with follow-up	683	482	364	220
Number (%) with IS AE	528 (77.3%)	349 (72.4%)	185 (50.8%)	104 (47.3%)
Injection site pain	509 (74.5%)	344 (71.4%)	169 (46.4%)	96 (43.6%)
Injection site swelling	158 (23.1%)	83 (17.2%)	31 (8.5%)	14 (6,4%)
Injection site erythema	147 (21.5%)	90 (18.7%)	48 (13.2%)	29 (13.2%)

Source: From Table 11-34, CSR 018v1, p. 263-4

Injection Site AEs and Dose

- Injection site AEs are noted in a higher proportion of subjects after dose 1 of the vaccine and placebo as compared to those seen after doses 2 and 3. (Source: Tables 11-35, 11-36, 11-37, CSR 018v1, p. 265-7, not shown here)

Injection Site AEs and Baseline Serostatus

- There is a slightly lower proportion of initially seropositive subjects with an injection site AE compared to those who were initially seronegative status, although the number

of those who are initially seropositive is small. (Source: Table 11-40 and 11-41, p. 270-1, CSR 018v1, not shown here)

Injection Site AEs at 6 Days ot Later after Vaccination

- A total of 6 subjects (3 in each group) experienced an injection site AE at 6 days or later after vaccination. Most were mild (one moderate in the vaccine group in a 15 year old male) and all recovered within hours to 5 days. (Source: Table 11-42, CSR 018v1, p. 272, not shown here)

Intensities of Injection site AEs

- A higher proportion of vaccine recipients reported an injection site AE of moderate (21.2%) to severe (5.2%) intensity compared with the placebo group (7.0% and 0.7%, respectively).
- A higher proportion of all injection site AEs were judged to be moderate (18.2%) to severe (3.3%) in the vaccine group as compared to the placebo group (8.7% and 0.6%, respectively). (Source: Tables 8-6 and 8-7, CSR 018v1, p. 151, not shown here)
- Among vaccine recipients, a higher proportion of girls reported their injection site AE to be moderate (26.1%) or severe (6.4%) as compared to boys (15.8% and 3.8%, respectively). There were similar results noted for the frequency of injection site AEs in vaccine recipients. (Tables 11-43, 11-45, p. 273, 275, CSR -18v1, not shown here)
- Among vaccine recipients, only a very slightly higher proportion of younger subjects reported an injection site AE as moderate (22.8%) or severe (5.4%) as compared to the older age group (18.9% and 4.8%, respectively). The frequency of intensity ratings were similar for the different age groups among vaccinees. (Tables 11-44 and 11-46, p. 274, 276, CSR 018v1, not shown here)
- Specific injection site AEs tended to be more common and more intense among subjects who received vaccine as compared to placebo recipients. (Source: Tables 8-8, 8-9. CSR 018v1, p. 152-3, not shown here)
- The frequency summary, by intensity rating, of all VRC prompted injection site AEs reported Days 1-5 after any vaccination visit is also presented. There are more moderate to severe ratings of pain, erythema, and swelling in the vaccine group as compared to the placebo group. When presented by gender, the girls have slightly more pain and swelling that are moderate to severe, but slightly less erythema that is moderate to severe than the boys among vaccine recipients. When presented by age, there is no clear trend in differences among the age groups. (Source: Tables 8-10, p. 154; Tables 11-53-, 11-54, p. 289-90, CSR 018v1, not shown here)

Systemic AEs (Days 1-15 after any vaccination)

- The most common systemic AEs in the 15 days after any vaccination visit were headache, pyrexia, and sore throat.
- The proportions of subjects in each group were very similar (vaccine and placebo). (See Table 237 below).

TABLE 237
Protocol 018: Number (%) of Subjects with Systemic AEs
Days 1-15 After Any Vaccination Visit

	Quadrivalent HPV Vaccine Recipients N=1179	Non-Alum Placebo Recipients N=594
Subjects with follow-up	1165	584
Number (%) with systemic AE	541 (46.4%)	260 (44.5%)
Headache	221 (19.0%)	110 (18.8%)
Pyrexia	100 (8.6%)	45 (7.7%)
Pharynolaryngeal pain	52 (4.5%)	24 (4.1%)
Diarrhea	43 (3.7%)	21 (3.6%)
Nausea	38 (3.3%)	22 (3.8%)
Abdominal pain upper	38 (3.3%)	17 (2.9%)
Nasopharyngitis	34 (2.9%)	22 (3.8%)
Myalgia	30 (2.6%)	10 (1.7%)
Vomiting	26 (2.2%)	18 (3.1%)
Dizziness	25 (2.1%)	9 (1.5%)
Arthralgia	21 (1.8%)	9 (1.5%)
Pain in extremity	19 (1.6%)	14 (2.4%)

Source: From Table 8-11, p. 157-8, CSR 018v1 and Table 4-13, Month 12 Safety Report,-018, p. 59-62

- There were no significant risk differences for systemic AEs reported Days 1-15 after any vaccination. (Source: Table 8-12, p. 159-60, CSR 018v1, not shown here)
- There were no significant risk differences for the systemic AEs prompted for by the VRC (which included muscle/joint pain, headaches, rashes/hives, and diarrhea). (Source: Table 8-13, p. 161, CSR 018v1, not shown here)
- In a summary of the number and percentage of subjects who reported a systemic AE Days 1-15 after any vaccination visit, within each gender group, the proportions of subjects reporting a systemic AE were comparable between vaccine recipients and placebo recipients.
- In both vaccination groups, the proportion of girls who reported a systemic AE appeared to be higher than the proportion of boys who reported such an AE. (See Table 238 below).

TABLE 238
Protocol 018: Number (%) of Subjects with Systemic AEs by Gender Within Each Vaccination Group (Days 1 -15 After Any Vaccination Visit)

	Quadrivalent HPV Vaccine Recipients		**Non-Alum Placebo Recipients**	
	Boys 9-15 years N=564	**Girls 9-15 years N=615**	Boys 9-15 years N=274	**Girls 9-15 years N=320**
Subjects with follow-up	557	608	269	315
Number (%) with systemic AE	**247 (44.3%)**	**294 (48.4%)**	**110 (40.9%)**	**150 (47.6%)**
Headache	90 (16.2%)	131 (21.5%)	42 (15.6%)	68 (21.6%)
Pyrexia	48 (8.6%)	52 (8.6%)	21 (7.8%)	24 (7.6%)
Pharynolaryngeal pain	25 (4.5%)	27 (4.4%)	10 (3.7%)	14 (4.4%)
Diarrhea	25 (4.5%)	18 (3.0%)	12 (4.5%)	9 (2.9%)
Nausea	14 (2.5%)	24 (3.9%)	7 (2.6%)	15 (4.8%)
Abdominal Pain upper	13 (2.3%)	25 (4.1%)	7 (2.6%)	10 (3.2%)
Nasopharyngitis	20 (3.6%)	14 (2.3%)	8 (3.0%)	14 (4.4%)
Myalgia	13 (2.3%)	18 (3.0%)	5 (1.9%)	5 (1.6%)
Vomiting	10 (1.8%)	16 (2.6%)	13 (4.8%)	5 (1.6%)
Dizziness	9 (1.6%)	16 (2.6%)	3 (1.1%)	6 (1.9%)
Arthralgia	9 (1.6%)	12 (2.0%)	5 (1.9%)	4 (1.3%)

Source: From Table 11-57, CSR 018v1, p. 298-311

- Within each age group, the proportions of subjects reporting a systemic AE were generally comparable between the vaccine and placebo groups, and systemic AEs were comparable across age groups. (Source: Table 11-58, p. 312-25, CSR 018v1, not shown here)

Muscukoskeletal AEs

Reviewer's Comment: Adverse events classified as Musculoskkleletal system were reviewed from the datasets for Protocol 018, comparing Gardasil recipients and saline placebo recipients. The proportions in the Gardasil and saline recipients were comparable. (See Table 239 below.)

TABLE 239
Protocol 018: Number (%) of Subjects With Musculsokeletal Adverse Events By Treatment Group (Days 1-15 After Any Vaccination) (Reviewer Constructed)

Musculoskeletal Event	Gardasil Recipients N=1179				Placebo Recipients N=579			
	n/%	Mild*	Moderate*	Severe*	n/%	Mild*	Moderate*	Severe*
Arthralgia, growing pains	21 (2%)	57.1%	33.3%	4.8%	11 (1.9%)	54.5%	36.4%	9.1%
Myalgia	31 (2.6%)	41.9%	48.4%	12.9%	10 (1.7%)	40%	60%	0
Pain Extremity	19 (16.1%)	63.2%	31.6%	5.3%	13 (22.5%)	69.2%	38.5%	0
Back Pain	11 (0.9%)	63.6%	36.4%	0	3 (0.5%)	100%	0	0
Joint swelling	1	--	--	100%	1	--	100%	--

*Proportion of subjects reporting mild, moderate, or severe grade for each AE.

- The majority of these musculoskeletal adverse events were of short duration.
- The majority of these AEs were of mild to moderate intensity.
- There was a higher proportion of subjects in the placebo group with arthralgias rated as severe in intensity (9.1%) as compared to the Gardasil recipients (4.8%).
- There was a higher proportion of Gardasil recipients with myalgia (12.9%) and pain in the extremity (5.3%) rated as severe as compared to the placebo group (0% for each AE).
- One subject in each of the vaccine and saline placebo group had a prolonged pain in the extremity (1.5 months – 1.84 months), but both resolved.
- There was one saline placebo recipient with mild muscle twitiching which was reported as continuing and not further specified.

Systemic AEs and Dose

- In both the vaccine and placebo groups, the proportion of subjects reporting a systemic AE after dose 1 was higher than those reporting an event after doses 2 and 3. The proportions of subjects in each group were comparable to each other after each dose. (Source: Tables 11-59, -60, -61, p. 326-9, CSR 018v1, not shown here)

Systemic AEs and Baseline Serostatus

- The proportions of subjects with a systemic AE were comparable among the subjects who were initially seronegative and seropositive, although the number of subjects in the latter group is small. (Source: Table 11-654, 11-65, p. 333-6, not shown here)

Intensities of Systemic AEs

- Most subjects who experienced a systemic AE reported them to be mild to moderate in intensity.
- There was no apparent difference in the proportion of subjects in either group reporting a moderate (20.1% vaccine, 20% placebo) or severe AE (5.9% vaccine, 6.3% placebo).
- The frequency of systemic AEs were also comparable among the treatment groups. (Source: Table 8-14, 8-15, p. 163, CSR 018v1, not shown here)
- The distribution of intensity ratings (classified by organ system) after each dose of vaccine were generally comparable, as well as overall. There was a slightly higher proportion of subjects with headache rated as severe in the Gardasil group (1.9%) compared to placebo (0.9%), and a slightly higher proportion with pyrexia rated as severe in the Gardasil group (0.9%) as compared to the placebo group (0.2%). (See discussion for pyrexia below) There was a slightly higher proportion of placebo recipient (1.2%) with abdominal pain rated as severe as compared to the Gardasil group (0.5%). (Source: Tables 11-67, 11-68, 11-69, p. 338-4; Table 8-16, p. 164-5, not shown here)

Temperatures (Days 1-5 after any vaccination)

- The proportion of subjects who reported an elevated temperature within 5 days of vaccination was slightly higher (by 0.6 percentage points) among subjects who received the quadrivalent HPV vaccine compared with placebo recipients. However, the difference was not statistically significant. (See Tables 240 and 241 below.)

TABLE 240
Protocol 018: Number (%) of Subjects with Elevated Ts
Days 1-5 After Any Vaccination Visit

	Quadrivalent HPV Vaccine N=1179	Placebo N=594
Subjects with f/u	1157	579
Maximum T (Oral)		
< 37.8 deg C	1074 (92.8%)	541 (93.4%)
>=37.8 deg C and < 38.9 deg C	67 (5.8%)	33 (5.7%)
>=38.9 deg C and < 39.9 deg C	13 (1.1%)	5 (0.9%)
>=39.9 deg C and < 40.9 deg C	2 (0.2%)	0 (0.0%)
>=40.9 deg C	1 (0.1%)	0 (0.0%)

Source: Table 8-17, CSR 018v1, p. 168

TABLE 241
Protocol 018: Comparison of Vaccination Groups with Respect to the Number of Subjects with Maximum oral T ≥ 37.8 deg C Days 1-5 After Any Vaccination Visit

	Gardasil N=1179	Placebo N=594	Risk Difference Vaccine minus Placebo	95% CI	p-value
Number of subjects with follow-up	1157	579			
Number of subjects with maximum T ≥ 37.8 deg C (≥ 100 deg F)	83 (7.2%)	38 (6.6%)	0.6	(-2.1, 3.0)	0.638

Percentages are calculated based on number of subjects with follow-up.
N=number of suibjects who received only the clinical material indicated.
n=number of subjects with indicated characteristics.
Source: Table 8-19, CSR 018v1, p. 170

- The proportions of girls and boys who reported an elevated temperature (37.8° C [100° F], oral or oral equivalent) within 5 days of vaccination were comparable. (See Table 242 below).

TABLE 242
Protocol 018: Number (%) of Subjects with Elevated T by Gender Within Each Vaccination Group Days 1-5 After Any Vaccination Visit

	Quadrivalent HPV Vaccine		Non-Alum Placebo	
	Boys 9-15 years of age N=564	Girls 9-15 years of age N=615	Boys 9-15 years of age N=274	Girls 9-15 years of age N=320
Subjects with follow-up	551	606	269	310
Max T				
< 37.8°C (< 100° F) or normal	510 (92.6%)	564 (93.1%)	254 (94.4%)	287 (92.6%)
≥ 37.8°C (≥ 100°F) and < 38.9°C (< 102°F)	34 (6.2%)	33 (5.4%)	13 (4.8%)	20 (6.5%)
≥ 38.9°C (≥ 102°F) and >39.9°C (< 103.8°F)	6 (1.1%)	7 (1.2%)	2 (0.7%)	3 (1.0%)
≥ 39.9°C (≥ 103.8°F) and < 40.9°C (< 105.6°F)	0	2 (0.3%)	0	0
≥ 40.9°C (≥ 105.6°F)	1 (0.2%)	0	0	0

Source: Table 11-70, CSR 018v1, p. 345

- The proportions of 9- to 12-year-old subjects and 13- to 15-year-old subjects who reported an elevated temperature within 5 days of vaccination were similar. Within each age group, the proportion of subjects who reported an elevated temperature within 5 days of vaccination was comparable between vaccine recipients and placebo recipients.

TABLE 243
Protocol 018: Number (%) of Subjects with Elevated T by Age Group Within Each Vaccination Group Days 1-5 After Any Vaccination Visit

	Quadrivalent HPV Vaccine		Non-Alum Placebo	
	Subjects 9-12 years of age	Subjects 13-15 years of age	Subjects 9-12 years of age	Subjects 13-15 years of age
Subjects with follow-up	679	478	361	218
Max T				
< 37.8°C (< 100° F) or normal	636 (93.7%)	438 (91.6%)	336 (93.1%)	205 (94.0%)
≥ 37.8°C (≥ 100°F) and < 38.9°C (< 102°F)	34 (5.0%)	33 (6.9%)	20 (5.5%)	13 (6.0%)
≥ 38.9°C (≥ 102°F) and < 39.9°C (< 103.8°F)	8 (1.2%)	5 (1.0%)	5 (1.4%)	0 (0.0%)
≥ 39.9°C (≥ 103.8°F) and < 40.9°C (< 105.6°F)	0	2 (0.4%)	0	0
≥ 40.9°C (≥ 105.6°F)	1 (0.1%)	0	0	0

Source: Table 11-71, CSR 018v1, p. 346

- There was no apparent difference in the incidences of Ts after doses 1, 2, and 3 of vaccine and placebo, and the incidences were comparable between the 2 groups. (Source: Tables 11-72, -73, -p74, CSR 018v1, p. 347-9, not shown here)

Reviewer's Comment: Narratives for the subjects with T's ≥ 39.9 °C were requested. In all age groups, theses fevers were of short duration and all subjects recovered. In the majority of these subjects, there was no fever reported after other doses of the vaccine or mild or moderate fever after other doses of the vaccine or placebo. In 2 Gardasil recipients with very high Ts recorded, repeat Ts within the same time period were reported as mild. In the placebo group, there were 2 subjects with very high Ts recorded, who were then reported to have moderate fever in the same time period.

Significant/Potentially Significant Events

Deaths: none

SAEs: There were 5 SAEs in vaccine recipients and none in placebo recipients. (See Table 244 below.)

TABLE 244
Protocol 018: SAEs (Vaccine Recipients)

AN	Age/Gender	Event	Days after dose	Duration	Recovered	Action taken
70380*	11 year old female	Anemia, dysfunctional uterine bleeding (severe)	11 days postdose 2	6 days	Yes	Received dose 3
70888	14 year old female	Appendicitis	4 days postdose 2	4 days	Yes	Received dose 3
71340*	15 year old male	Acute renal failure (Surgery for broken finger with multiple meds 5 days postdose 1)	6 days postdose 1	16 days	Yes	Did not receive further doses
71662*	13 year old male	Insulin dependent diabetes mellitus (had an elevated glucose on the day of vaccination)	4 days postdose 1	Ongoing	On treatment	Received 3 doses
71928	13 year old male	Infected toe with pain toe	2 days postdose 2	5 days	Yes	Received dose 3

*Case summaries below for selected subjects.

- **AN 71340**, broke his finger 5 days after dose 1, required surgery, and developed renal failure. At the time of the operation, he received sufentanil citrate (opioid), lidoacine, tetanus toxoid, bupivicaine hydrochloride + lidocaine ketorolac (anti-inflammatory; renal impairment seen after longer term use) and dipyrone (anti-inflammatory). The day after surgery, he was nauseous and vomiting and was noted to have an elevated BUN and Cr. He was treated with lasix and metoclopramide, and by days 21 had recovered from the renal failure.
- **AN 70888**, received vaccine and experienced abdominal pain 3 days after receiving Dose 2. She was treated with acetaminophen and ibuprofen. The subject was diagnosed with appendicitis 4 days after receiving Dose 2. She was admitted to the hospital for removal of the appendix 7 days after receiving Dose 2. The subject recovered and was discharged from the hospital 8 days after receiving Dose 2. The reporting investigator determined that appendicitis was probably not related to study vaccine/placebo

- **AN 71662,** the subject with IDDM, appears to have had an elevated glucose on the day of vaccination, and a Hb A1C was reported as elevated at the time of vaccination (although it may have been on the upper limit of normal).
- **AN 70380**, had dysfunctional uterine bleeding and anemia, which may occur near the onset of menses.
- **AN 71928,** developed an infected toe and pain in his right toe and was taken to the hospital 2 days after receiving Dose 2. Laboratory tests performed revealed an elevated white blood cell (12.5 10^9/L), neutrophil (increased) and C-reactive protein count (127 mg/L). The subject recovered from the pain and was discharged from the hospital with instructions to soak the toe in soap and water three times a day. Repeat laboratory tests were performed 5 days after receiving Dose 2. The subject recovered. The reporting investigator determined that the pain in right toe and infected toe were definitely not related to study vaccine/placebo.

Subjects who discontinued due to an AE: 3 subjects
- **AN 71340** (the subject above with acute renal failure).
- **AN 71264:** 14 year old female had 4 inch swelling day 1 after dose 2. This lasted 5 days. She did not receive further vaccine, but did continue follow-up in the study. (**Investigator attribution**: vaccine related.)
- **AN 71945:** 11 year old male had moderate injection site pain 1 day after the first dose of vaccine, and this lasted 6 hours. He did not receive additional vaccine. (**Investigator attribution:** possibly vaccine related.)

Comparison of severe injection site AEs in vaccination groups (Days 1-5)
- The percentage of subjects who reported a severe injection site AE Days 1-5 after any vaccination visit was statistically higher in the vaccine group (5.0%) as compared to the placebo group (0.7%). The risk difference was 4.5% (95% CI: 3.0, 6.0%). (Source: Table 8-23, CSR 018v1, p. 179, not shown here)

New Medical Conditions
- The proportions of subjects with new medical conditions through Month 7 were comparable between the vaccination and placebo groups.
- The most common new medical conditions during this time period were headache and URI. (Source: Table 8-24, CSR 018v1, p. 181-2, not shown here)
- There was one case of autoimmune thyroiditis in the vaccine group and none in the placebo group. The sponsor provided additional information about this condition in general and across studies. A discussion is included in the safety summary in this document. (Source: Table 11-79, CSR 018v1, p. 354-63, not shown here)

Pregnancies and Outcome: There were no pregnancies in this study.

Follow-up from Month 7 to Month 12
- Subjects (guardians) were contacted at Month 12 of the study to assess for any new medical conditions.
- Overall, 95.0% of subjects randomized (95.3% Gardasil group and 94.4% of placebo group) entered the Persistence Phase of Protocol 018. Five subjects discontinued from

the study (3 in the vaccine group: 2 lost to follow-up and 1 withdrew consent; 2 in the placebo group due to relocation).

- A lower proportion of vaccine recipients (29.0%) reported a new medical condition between Day 1 and Month 12 as compared to placebo recipients (31.0%). This was also noted in new medicalo conditions between Month 7 and Month 12. See Tables 245 and 246 below).
- There were no new SAEs reported in this period.

TABLE 245
Protocol 018: New Medical Conditions Day 1 through Month 12

Subjects in analysis population	Gardasil N=1128	Placebo N=562
Subjects with new medical history	327 (29.0%)	174 (31.0%)
GI	43 (3.6%)	30 (5.1%)
Abdominal Pain	8 (0.7%)	8 (1.3%)
Immune	21 (1.8%)	9 (1.5%)
Seasonal allergy	12 (1.0%)	5 (0.8%)
Infection	265 (22.5%)	150 (25.3%)
Influenza	20 (1.7%)	13 (2.2%)
Nasophrayngitis	26 (2.2%)	21 (3.5%)
Pharyngitis	30 (2.5%)	13 (2.2%)
Tonsillitis	12 (1.0%)	10 (1.7%)
URI	41 (3.5%)	15 (2.5%)
Musculoskeletal and CTD	53 (4.5%)	27 (4.5%)
Arthralgia	15 (1.3%)	7 (1.2%)
Neoplasm	11 (0.9%)	7 (1.2%)
Neurological	66 (5.6%)	36 (6.1%)
Headache	58 (4.9%)	30 (5.1%)
Psych	16 (1.4%)	10 (1.7%)
Reproductive and Breast Disorders	24 (2.0%)	7 (1.2%)
Respiratory	54 (4.6%)	32 (5,4%)
Cough	12 (1.0%)	10 (1.7%)
Pharynolaryngeal pain	16 (1.4%)	7 (1.2%)
Skin	46 (3.9%)	28 (4.7%)
Surgical and medical Procedures	36 (3.1%)	17 (2.9%)

Source: Table 4-5, Month 12 Safety Report-018, p. 28-30

TABLE 246
Protocol 018: New Medical Conditions Month 7 through Month 12

Subjects in analysis population	Gardasil N=1128	Placebo N=562
Subjects with new medical history	327 (29.0%)	174 (31.0%)
GI	31 (2.7%)	18 (3.2%)
Infection	192 (17.0%)	96 (17.1%)
Influenza	32 (2.8%)	18 (3.2%)
Nasophrayngitis	20 (1.8%)	8 (1.4%)
Pharyngitis	30 (2.7%)	9 (1.6%)
Tonsillitis	6 (0.5%)	7 (1.2%)
URI	19 (1.7%)	11 (2.0%)
Musculoskeletal and CTD	25 (2.2%)	14 (2.5%)
Neoplasm	7 (0.6%)	6 (1.1%)
Psych	7 (0.6%)	6 (1.1%)
Reproductive and Breast Disorders	12 (1.1%)	5 (0.9%)
Respiratory	22 (2.0%)	19 (3.4%)
Pharynolaryngeal pain	4 (0.4%)	6 (1.1%)
Skin	27 (2.4%)	19 (3.4%)
Surgical and medical Procedures	10 (0.9%)	7 (1.2%)

Source: Table 4-6, Month 12 Safety Report, p. 31-3

Comments-Conclusion Regarding Data for Protocol 018 (Reviewer's Opinion)

- Protocol 018 provides saline placebo-controlled safety data for subjects 9-15 years of age (617 girls and 567 boys who received vaccine). This is of particular interest because the other studies used alum placebo as a safety comparison.

- **Safety**
  - Overall, there was a higher proportion of vaccine recipients with an AE as compared to placebo recipients, and appears to be due to a higher proportion of Gardasil recipients with an injection site AE.
  - There was a higher proportion of vaccine recipients with an injection site adverse event compared to placebo recipients.
    - There were statistically significant differences with regards to injection site pain, swelling, and erythema between the vaccine and placebo recipients.
    - There was a higher proportion of vaccinees with a moderate or severe injection site AE compared to placebo recipients, and there was a statistically higher risk of a vaccine recipient experiencing a severe injection site AE as compared to placebo recipients.
    - The 9-15 year old girls had a slightly higher proportion of injection site AEs compared to 9-15 year old boys.
    - There was a higher proportion of subjects with an injection site AE overall after dose 1 compared to doses 2 and 3, although there may have been more severe swelling and erythema after doses 2 and 3 compared to dose 1.
  - The proportion of vaccinees and placebo recipients with systemic adverse events was similar.
    - Most systemic AEs were mild to moderate in intensity.
    - There was a higher proportion of subjects with a systemic AE after dose 1 compared to dose 2.

- There was a slightly higher proportion of girls with a systemic AE when compared to boys who had received the same study material.
- The rates of elevated Temperatures were similar between the vaccine and placebo groups, the girls and boys, and the 9-12 year olds compared to the 13-15 year old subjects, although there was a slightly higher proportion of Gardasil recipients with a T $\geq$ 39.9°C ($\geq$ 103.8°F) [0.5%] as compared to placebo recipients [0.0%].
- Two of the subjects discontinued due to local injection site reaction.
- The 5 SAEs noted in the vaccine group were not clearly related to vaccine administration.

- **Immunogenicity**
  - The vaccine was immunogenic in both the girls and boys of this age group.
  - The objective was to demonstrate that the immune response in boys was not inferior to that in girls (GMT ratios and seroconversion rates). The immune responses in boys were noted to be non-inferior to those in girls 9-15 years of age (by GMT comparison and seroconversion comparison).

9. Overview of Efficacy Across Trials

9.1.1 Methods

Indication: Prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine (6, 11, 16, and 18):

Cervical Cancer
Cervical adenocarcinoma *in situ* (AIS)
Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
Cervical intraepithelial neoplasia (CIN) grade 1
Genital warts (condyloma acuminata)

Population: Females 9-26 years of age

The clinical data used to support efficacy for cervical lesion indication came from Study 015, and the combined efficacy results from Studies 005, 007, 013 and 015.
The clinical data used to support efficacy for the External Genital Lesion (EGL) related indications came from Study 013, as well as from Studies 015 and 007.

9.1.2 General Discussion of Efficacy Endpoints

HPV 16/18 related Cervical cancer, cervical AIS, Cervical Intraepithelial Neoplasia Grades 2 and 3: The use of the CIN 2/3, AIS or worse with HPV detection to support a cervical cancer indication was discussed at the VRBPAC meeting in November 2001. Members agreed that these were clinically relevant and feasible endpoints to evaluate for evidence of efficacy of Gardasil against squamous cell or adenocarcinoma of the cervix.

9.1.3 Efficacy Endpoints

The analyses from combined studies for indications sought are next reviewed. Analyses from individual studies were discussed earlier in the review within the specific study.

Primary Efficacy Endpoint

- **HPV 16/18 related Cervical cancer, CIN 2/3, AIS, or worse:** There were no cases of cervical cancer. As noted above, CIN 2/3 or worse and AIS are used as surrogate endpoints for indication of prevention of squamous cell cancer and adenocarcinoma of the cervix. This endpoint was the primary endpoint in Study 015 (discussed previously in Section 8.1, Efficacy Outcomes) and in a pre-specified combined analysis across Studies 005, 007, 013, and 015. An analysis for 16/18 related CIN 2/3, AIS, or worse was performed in August 2005, and at this time, 21 cases had accrued in Protocol 015 and 53 cases in the combined studies meeting the protocol specified criterion for the total number of cases (48) required for the final analysis.

Additional Exploratory Endpoints Evaluated

- **HPV 6, 11, 16, or 18 related CIN 2/3, AIS, or worse:** This was a secondary endpoint in Study 015 and a supplemental endpoint in combined studies 005, 007, 013, and 015.
- **HPV 6, 11, 16, or 18 related Condyloma Acuminata:** This was a component of a co-primary composite endpoint in Study 013 and evaluated in combined studies 007, 013, and 015.

- **HPV 6, 11, 16, or 18 related VIN 2/3 or VaIN 2/3:** This was a component of a co-primary composite endpoint in Study 013, and evaluated in combined studies 007, 013, and 015.
- **HPV 6, 11, 16, or 18 related CIN 1:** This was a component of a co-primary composite endpoint of cervical dysplasia in Study 013, and a supplemental endpoint in combined studies 005, 007, 013, and 015.
- **HPV 6, 11, 16, or 18 related VIN 1 and VaIN 1:** This was evaluated in Study 013 and in combined studies 007, 013, and 015.

Analysis Populations

Several analysis populations were used to assess efficacy of Gardasil against pre-defined and exploratory histopathological endpoints. These are reviewed here.

- **The Per Protocol for Efficacy (PPE) population** included subjects who were not protocol violators, were naïve (PCR negative cervicovaginal sample and seronegative) to the specific vaccine HPV type through Month 7 for which efficacy was being assessed. Subjects could have had an abnormal Pap smear at baseline. Efficacy analyses were specific to the HPV type, for example, a subject randomized to receive Gardasil with evidence of HPV infection type 16 by PCR detection of HPV 16 DNA at the baseline visit and subsequent diagnosis of CIN 3 disease with virologic evidence of HPV 16 would be excluded from the efficacy analysis for HPV type 16. This subject would be included in the per protocol efficacy population for HPV 18 because she did not meet exclusion criteria for the per protocol population for HPV 18. Therefore, because she contributed favorable efficacy data for HPV 18 "incidence rate per 100 person years at risk", she ultimately contributed favaorable primary endpoint efficacy data for the overall per protocol population for HPV 16/18. For the composite HPV 16/18 related CIN 2/3, AIS or worse endpoint, an individual could only contribute one case. Subjects in Study 005 were administered HPV 16 vaccine only, thus only HPV 16 related endpoints were evaluated. See **APPENDIX 6** for further details.
- **The MITT-1 population** included subjects who met criteria for inclusion in the PPE as well as protocol violators.
- **The MITT-2 population** included subjects who met the criteria for inclusion in the MITT-1 population but cases were counted beginning 30 days after dose 1.
- **The MITT-3 population** included all subjects, regardless of baseline HPV PCR and serostatus. Cases were counted after 30 days after dose 1.
- **The Restricted MITT-2 population** included subjects seronegative and PCR negative for all 4 vaccine HPV types with a negative Pap test at baseline. Cases were counted beginning at 30 days after dose 1.
- **The Restricted MITT-3 population** included subjects regardless of baseline HPV PCR and serostatus and a negative Pap test at baseline. Cases were counted beginning 30 days after dose 1.

9.1.4
Study Design Across Trials

20, 887 subjects were enrolled in Studies 005, 007, 013, and 015. These studies were similar in design:

- They were all double-blind, randomized, placebo-controlled studies. In Study 005, monovalent HPV 16 vaccine was administered [40 mcg L1 VLP] (which was bridged to the HPV 16 component of the quadrivalent vaccine in substudy 012 of Protocol 013). In the other studies, efficacy of Gardasil was assessed.
- Inclusion/exclusion criteria were similar.
- The vaccine was administered using a 0, 2 and 6 months schedule in all studies.
- In studies 005, 007, and 013, subjects visited the clinic for gynecological exams approximately every 6 months. In study 015, clinic visits were every 6 months in the first year and thereafter annually.
- Efficacy was evaluated in females 16-23 years of age in Protocols 005, 007, and 013, and in females 16-26 years of age in Protocol 015 (Singapore).
- The median age of subjects was 20 years in all trials.
- The subjects were to have $\leq$ 4 lifetime sexual partners in Protocols 007, 013, and 015, and $\leq$ 5 lifetime sexual partners in Protocols 005.
- ThinPrep Pap tests were used in all 4 trials. In Protocol 005, they were read at 5 regional labs. In the other studies, there were read at ----------.
- In all studies, the minimal Pap test referral for colposcopy was ASC-US (with use of Hybrid Capture II testing to identify high risk HPV types in Protocols 007, 013, and 015).
- There were similar colposcopy algorithms for the 4 trials (see Appendices for details), and the algorithms were mandatory in Protocol 013 and 015. In Protocol 015 the algorithm permitted ASC-US and LSIL to be followed with a repeat Pap smear in 6 months rather than an immediate colposcopy to allow low grade lesions to regress, and to conform with international standards. The exception was LSIL noted at baseline or Month 48 (study end), in which case the subject would be referred immediately for colposcopy.
- For study endpoint purposes, all histology slides were read by a pathology panel of experts in the field of cervical cancer. The members of the pathology panel were blinded to the central lab diagnoses, study group assignment, and the PCR status. There was a well-defined standard operating procedure in place to handle cases where there was disagreement as to the diagnosis. Please refer to **APPENDIX 2** for more details.

9.1.5
Subject Demographics across studies

With the exception of Study 005 which enrolled subjects from North America, the other studies had sites in Latin America and Europe. Studies 013 and 015 also had sites in the Asia Pacific region. Table 247 provides the proportions of subjects enrolled into each study by region.

TABLE 247
Number of Subjects Enrolled: Distribution by Region

Subjects	Protocol 005	Protocol 007	Protocol 013	Protocol 015	Total for each region
North America	2391 (100%)	251 (45.6%)	1713 (29.8%)	913 (7.5%)	5266 (25.3%)
Latin America	0	187 (33.9%)	2278 (39.6%)	3191 (26.2%)	5606 (27.0%)
Europe	0	113 (20.5%)	1189 (20.7%)	7872 (64.8%)	9174 (44.1%)
Asia-Pacific	0	0	566 (9.9%)	181 (1.5%)	747 (3.6%)
Total each study	2391	551	5746	12157	20793

Source: Table 2.7.3-cervixcancer: 9, p. 66

A summary of baseline characteristics of Study 005, 007, 013, and 015 subjects administered Gardasil, HPV 16 vaccine, or placebo is shown in Table 248. The median number of sexual partners was 2 for the Gardasil and placebo groups, and 3 for the HPV 16 monovalent vaccine group.

TABLE 248
Protocols 005, 007, 013, and 015: Summary of Enrolled Subject Characteristics by Vaccination Group

	Gardasil N=9087	HPV 16 vaccine N=1508	Placebo N=10292	**Total N=20887**
Age (years)				
Mean	20.0	20.1	20.0	**20.0**
Range	15-26	16-25	13-26	**13-26**
BMI				
Mean	22.9	24.1	23.1	**23.1**
Race/Ethnicity				
Asian	309 (3.4%)	96 (6.4%)	384 (3.7%)	**789 (3.8%)**
Black	332 (3.7%)	99 (6.6%)	526 (5.1%)	**957 (4.6%)**
Hispanic American	1136 (12.5%)	182 (12.1%)	1236 (12.0%)	**2554 (12.2%)**
Native American	13 (0.1%)	11 (0.7%)	26 (0.3%)	**50 (0.2%)**
White	6400 (70.4%)	1089 (72.2%)	7211 (70.1%)	**14700 (70.4%)**
Other	897 (9.9%)	31 (2.1%)	909 (8.8%)	**1837 (8.8%)**
Region				
Asia-Pacific	349 (3.8%)	46 (3.1%)	353 (3.4%)	**748 (3.6%)**
Europe	4557 (50.1%)	68 (4.5%)	4556 (44.3%)	**9181 (44.0%)**
Latin America	2800 (30.8%)	71 (4.7%)	2795 (27.2%)	**5666 (27.1%)**
North America	1381 (15.2%)	1323 (87.7%)	2588 (25.1%)	**5292 (25.3%)**
Smoking Status				
Current smoker	2418 (26.6%)	372 (24.7%)	2780 (27.0%)	**5570 (26.7%)**
Ex-smoker	647 (7.1%)	203 (13.5%)	907 (8.8%)	**1757 (8.4%)**
Never smoked	6018 (66.2%)	919 (60.9%)	6593 (64.1%)	**13530 (64.8%)**
Missing or unknown	4 (0.0%)	14 (0.9%)	12 (0.1%)	**30 (0.1%)**

N=number of subjects randomized
n=numer of subjects with the indicated characteristic
Source: Summary of Efficacy-cervixcancer: Table 14, p. 86-7

The number of subjects enrolled in each age group is shown below. With the exception of Study 015 which enrolled subjects 16-26 years of age, the other studies enrolled subjects 16-23 years of age. As noted in Table 248 above, the mean age of subjects administered Gardasil was approximately 20 years of age.

TABLE 249
Protocols 005, 007, 013, 015: Number of Subjects Entered by Age Category: All Randomized Subjects

	Gardasil	HPV 16	Placebo
Age (years)	N=9087	N=1508	N=10292
12-13	0	0	1
14-15	1	0	1
16-17	1152	50	1181
18-19	2364	571	2855
20-21	2935	546	3439
22-23	2589	338	2778
OVER 23	46	3	37
Mean	20.0	20.1	20.0

N=number of subjects randomized in the vaccination group
n=number of subjects within category
Source: From Summary of Efficacy-cervixcancer, Appendix 14, p.290

Pap Test Abnormalities at Baseline

Overall, in the 4 studies, 12% of subjects had squamous intraepithelial lesions noted on their Day 1 Pap smear. The majority of these were LSIL (5.9%) and ASC-US (5%). (See Table 250 below.)

TABLE 250
Protocols 005, 007, 013 and 015: Summary of Pap Test Results at Day 1 by Vaccination Group – Efficacy Population

	Gardasil N=9087	HPV 16 Vaccine N=1508	Placebo N=10292	Total N=20887
Subjects with Day 1 Pap Test Results	8992	1494	10174	20660
Day 1 Pap test Result = Satisfactory*	8831 (98.2%)	1470 (98.4%)	9987 (98.2%)	20288 (98.2%)
SIL Present**	1018 (11.5%)	210 (14.3%)	1198 (12.0%)	2426 (12.0%)
ASC-US	398 (4.5%)	98 (6.7%)	528 (5.3%)	1024 (5.0%)
ASC-H	28 (0.3%)	1 (0.1%)	25 (0.3%)	54 (0.3%)
LSIL	524 (5.9%)	96 (6.5%)	585 (5.9%)	1205 (5.9%)
HSIL	62 (0.7%)	14 (1.0%)	55 (0.6%)	131 (0.6%)
Atypical glandular cells	6 (0.1%)	0 (0.0%)	4 (0.04%)	10 (0.5%)
AIS	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)

*Percentage calculated based on number of subjects with satisfactory Pap test
**Percentages of SIL calculated based on number of subjects with a satisfactory Pap test at Day 1
N=number of subjects randomized
Source: Table 2.7.3-cervix cancer:21, Summary of efficacy-cervix cancer, p. 104

Vaccine HPV Status at Baseline

Overall, 27% of subjects were seropositive and/or PCR positive to one or more of the vaccine HPV types at baseline.

TABLE 251
Protocols 007, 013, and 015: Composite HPV 6, 11, 16, and 18 Status by PCR and/or Serology at Day 1 by Vaccination Group

Day 1 Composite HPV 6/11/16/18 Status	Gardasil N=9087	HPV 16 Vaccine N=304	Placebo N=9087	Total N=18,478
	m/n (%)		m/n (%)	m/n (%)
Negative to HPV 6, 11, 16, and 18 By serology and PCR	6531/8968 (72.8%)	228/301 (75.7%)	6562/8982 (73.1%)	13321/18251 (73.0%)
Positive to HPV 6, 11, 16, and 18 By serology and PCR	2437/8968 (27.2%)	73/301 (24.3%)	2420/8982 (26.9%)	4930/18251 (27.0%)

N=number of subjects randmozied
n=number of subjects with non-missing data
m=number of subjects in the respective category
Source: Table 2.7.3-cervix cancer:22, Summary of efficacy-cervix cancer, p. 107

Exposure to More than One Vaccine HPV type by HPV PCR status at day 1
Among subjects included in the efficacy analyses 1-2% in each group had evidence of two or more vaccine HPV tyoes detected by PCR at baseline.

TABLE 252
Protocols 005, 007, 013, and 015: Number of HPV Types Detected by PCR at Day 1 by Vaccination Groups – Randomized Subjects

Number of HPV types Detected by PCR at Day 1	Gardasil N=9087		HPV 16 L1 VLP N=1508		Placebo N=10292		Total N=20887	
	n	m	n	m	n	m	n	m
At least 2 types detected	9068	217 (2.4%)	304	4 (1.3%)	9070	199 (2.2%)	18442	420 (2.3%)
Exactly 2 types detected	9068	201 (2.2%)	304	4 (1.3%)	9070	184 (2.0%)	18442	389 (2.1%)
Exactly 3 types detected	9067	15 (0.2%)	304	0 (0.0%)	9070	15 (0.2%)	18441	30 (0.2%)
Exactly 4 types detected	9064	1 (0.01%)	304	0 (0.0%)	9069	0 (0.0%)	18437	1 (0.01%)

N= number of subjects randomized
n=number of subjects who have non-missing PCR results at Day 1 for at least the number of types indicated
m= number of subjects in the respective category
Source: Table 2.7.3:25, Summary of Clinical Efficacy – cervix cancer, p. 111

Subject Disposition
The number of subjects enrolled who received at least one does of vaccine or placebo and reasons for exclusion from the PPE population are noted in Table 253. The most common reason for exclusion from the PPE population was seropositivity to the relevant HPV type. Overall, 66-75% of enrolled subjects were included in the PPE population analysis for the relevant HPV type.

TABLE 253
Protocols 005, 007, 013, 015: Subject Accounting for the Efficacy Analysis Populations by Vaccination Group

	Gardasil	HPV 16 vaccine	Placebo	Total
Number Enrolled	9087	1508	10292	20887
Number of subjects who received at least 1 vaccination (a)	9075	1497	10273	20845
Excluded from Per Protocol Efficacy Population				
HPV 6/11 (b)	2109	N/A	2183	4292
HPV 16	2393	514	3008	5915
HPV 18 (b)	1626	N/A	1692	3318
Included in Per Protocol Efficacy Analysis				
HPV 6/11 (b)	6966	N/A	6892	13858
HPV 16	6682	983	7265	14930
HPV 18 (b)	7449	N/A	7383	14832
Reasons for Exclusion (c)				
General Protocol Violation	583	213	743	1539
Incorrectly randomized	7	3	7	17
Enrolled in another trial	0	0	2	2
Enrolled more than once	1	1	0	2
Incorrect study material or dose amount	29	6	33	68
Incomplete vaccination	262	185	383	830
Received nonstudy vaccination (d)	96	16	102	214
Received immunosuppressives, IgG, or blood	89	7	100	196
History of immune disorder	6	0	7	13
History of genital warts or genital warts at Day 1 (e)	2	0	3	5
Vaccine Temperature out of range	40	0	38	78
Vaccine series not completed within 12 months	75	5	95	175
Ablative surgery prior to Day 1	3	0	0	3
Vaccine administered in buttocks	0	0	1	1
Subject had 2 cervices	2	0	1	3
Subject prematurely unblinded	5	1	2	8
Missing Day 1 serum samples/results	9	0	9	18
Day 1 serum out of acceptable day range	12	3	7	22
Missing Day 1 swab sample/results	176	18	145	339
Day 1 swab sample out of acceptable day range	3	0	4	7
Missing Month 3 swab sample/results	148	18	170	336
Missing Month 7 swab sample/results	232	46	217	495
Month 7 swab sample out of acceptable day range (f)	169	30	200	399
Positive to HPV 6 or 11 (b) (g)				
At Day 1	1092	N/A	1099	2191
After day 1, at or before Month 7	1214	N/A	1333	2547
Positive to HPV 16 (g)				
At Day 1	1439	261	1679	3379
After day 1, at or before Month 7	1537	284	2029	3850
Positive to HPV 18 (b) (g)				
At Day 1	574	N/A	572	1146
At or before Month 7	655	N/A	773	1428

(a) Subjects who did not receive at least 1 vaccine were excluded from analysis population.
(b) Counts do not include Protocol 005 which does not contribute to analyses of endpoints related to HPV 6, 11, and 18

(c) Subjects are counted once in each exclusion category. A subject may appear in more than one category.
(d) Includes live vaccines received within 21 days before or 14 days after study vaccine or inactivated or recombinant vaccine within 14 days of study vaccine.
(e) Applies to Protocol 013 only (Note: There was one subject in Protocol 015 not randomized because of genital warts, and none reported in Protocol 007).
(f) Among subjects who received all 3 vaccinations.
(g) Applies only to the analysis populations for the respective HPV type(s).
Source: Summary of Efficacy-cervixcancer: Table 13, p. 82-4

Subject follow-up
For each of the endpoints efficacy was calculated using incidence per 100 person years. As noted in Table 254 below the mean duration of follow-up was variable in each study.

TABLE 254
Protocols 005, 007, 013, 015: Number of Subjects, Median Age, and Duration of Follow-up in Efficacy Population (Original BLA submission)

Subjects	Protocol 005	Protocol 007	Protocol 013	Protocol 015
N	2391	551	5442	12157
# Vaccine	1193	276	2717	6082
# Placebo	1198	275	2725	6075
Mean Age (Range)	21.5 yr. (16-25)	20.5 yr. (13-24)	20.3 yr. (16-24)	19.9 yr. (15-26)
Mean duration of follow-up*	3.1 years	2.4 years	1.7 years	1.4 years

Source: CSR 007, Table 7-2 and 2.7.3-cervixcancer Table 2.7.3:8
*Protocols 013 and 015 were ongoing. Mean duration of follow-up calculated based on all visits completed as of 7/13/05 for Protocol 013 and 6/10/05 for Protocol 015.
Total number of subjects with data for cervical disease efficacy = 20541

9.1.6 Vaccine Efficacy

Cervical Intraepithelial Neoplasia and Cervical Adenocarcinoma in situ

Efficacy against HPV 16/18 related CIN 2/3, AIS, or worse
Table 255 presents the combined analysis of efficacy of Gardasil against HPV16/18 related CIN2/3 or worse or AIS for the PPE, MITT-1, MITT-2 and MITT-3 populations. In the PPE population the observed vaccine efficacy against HPV 16/18 related CIN 2/3 or worse is 100% (95% CI: 92.9, 100%). In the MITT-1 population, which included protocol violators, efficacy was 100% (95% CI: 93.4, 100%). When efficacy was evaluated in the MITT-2 population (similar to MITT-1 but cases were counted starting 30 days after the first immunization) vaccine efficacy remained high (98.8%, 95% CI: 92.9, 100%). The one case that occurred was an HPV 16 related CIN 2 that developed by Month 7. Of note, when efficacy of Gardasil is evaluated in subjects regardless of baseline PCR or serostatus (the MITT-3 population) the observed efficacy is markedly reduced (39.0%, 95% CI: 23.3, 51.7%) as compared to efficacy in subjects seronegative and PCR negative at baseline. Efficacy of Gardasil in the MITT-3 population may more closely represent the expected efficacy in the population of young US women than efficacy estimates in the naive populations.

TABLE 255
Protocols 005, 007, 013, 015: Analysis of Efficacy Against HPV 16/18 Related CIN 2/3, AIS or Worse

	Gardasil or HPV 16 vaccine N=10268				Placebo N=10273					
Study Population HPV 16/18 related CIN 2/3, AIS or worse	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	8847	0	14178.1	0.0	8460	53	14060.6	0.4	**100.0%**	(92.9, 100%)
MITT-1, combined	8957	0	14855.0	0.0	8943	57	14741.7	0.4	**100.0%**	(93.4, 100%)
MITT-2, combined	9342	1*	19970.1	0.0	9400	81	20029.8	0.4	**98.8%**	(92.9, 100%)
MITT-3, combined	9831	122	21107.3	0.6	9896	201	21228.4	0.9	**39.0%**	(23.3, 51.7%)

*Occurred in Protocol 015
N=number of subjects randomized to the respective vaccination group who received at least one injection
n=number of subjects who have at least one follow-up visit after Month 7 in the PPE and MITT-1 population, following 30 days after Day 1 in the MITT-2 and MITT-3 population.
Source: From Table 2.7.3-cervixcaxncer: 29, p. 127-8

Estimates of efficacy in the MITT-3 population for the individual studies as well as the combined studies were provided by the sponsor. The sponsor notes that the point estimate of efficacy increases with longer follow-up time following vaccination. (See Table 256 below). In the MITT-3 population of Study 005, in which the mean duration of follow-up was 3.1 years, vaccine efficacy against HPV 16/18 related CIN 2/3 or worse in the MITT-3 population was 77.9% (95% CI: 40.6, 93.4%) compared to efficacy in Study 015 (39.2% [95% CI: 16.9, 55.8%]) in which the mean duration of follow-up was 1.4 years. This difference may be due to a decline in the proportion of cases due to baseline disease or infection over time. However, it should be noted that the 95% CIs on the estimates of vaccine efficacy for these analyses overlap. Thus, it is difficult to draw a definitive conclusion for these data. Additional follow-up of subjects is necessary to evaluate whether this is a valid conclusion.

TABLE 256
Protocols 005, 007, 013, 015 (Combined and Separately): Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse –MITT-3 Population

	Gardasil or HPV 16 vaccine N=10268				Placebo N=10273					
Study Population HPV 16/18 related CIN 2/3 or worse	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
MITT-3 (combined)	9831	122	21107.3	0.6	9896	201	21228.4	0.9	**39.0%**	(23.3, 51.7%)
By Protocol										
005	1017	5	3640.3	0.1	1050	23	3699.9	0.6	**77.9%**	(40.6, 93.4%)
007	260	2	722.9	0.3	262	7	714.2	1.0	**71.8%**	(<0.0, 97.1%)
013	2607	48	5585.0	0.9	2611	60	5570.4	1.1	**20.2%**	(<0.0, 46.6%)
015	5947	67	11159.5	0.6	5973	111	11243.9	1.0	**39.2%**	(16.9. 55.8%)

N=number of subjects randomized to the respective vaccination group who received at least one injection
n=number of subjects who have at least one follow-up visit after following 30 days after Day 1 in the MITT-3 population. Source: From Table 2.7.3-cervixcaxncer: 29, p. 127-8

Efficacy Against HPV 6, 11, 16, or 18 related CIN 2/3, AIS, or worse (combined analysis):

The sponsor provided an exploratory analysis of cases of all CIN due to any of the HPV types contained in the vaccine. There is evidence for efficacy in both the PPE and MITT-2 population however, when analysis is expanded to include cases in subjects seropositive and/or PCR positive at baseline (MITT-3), the estimate of efficacy decreases to 46.4% (95% CI: 35.2, 55.7%).

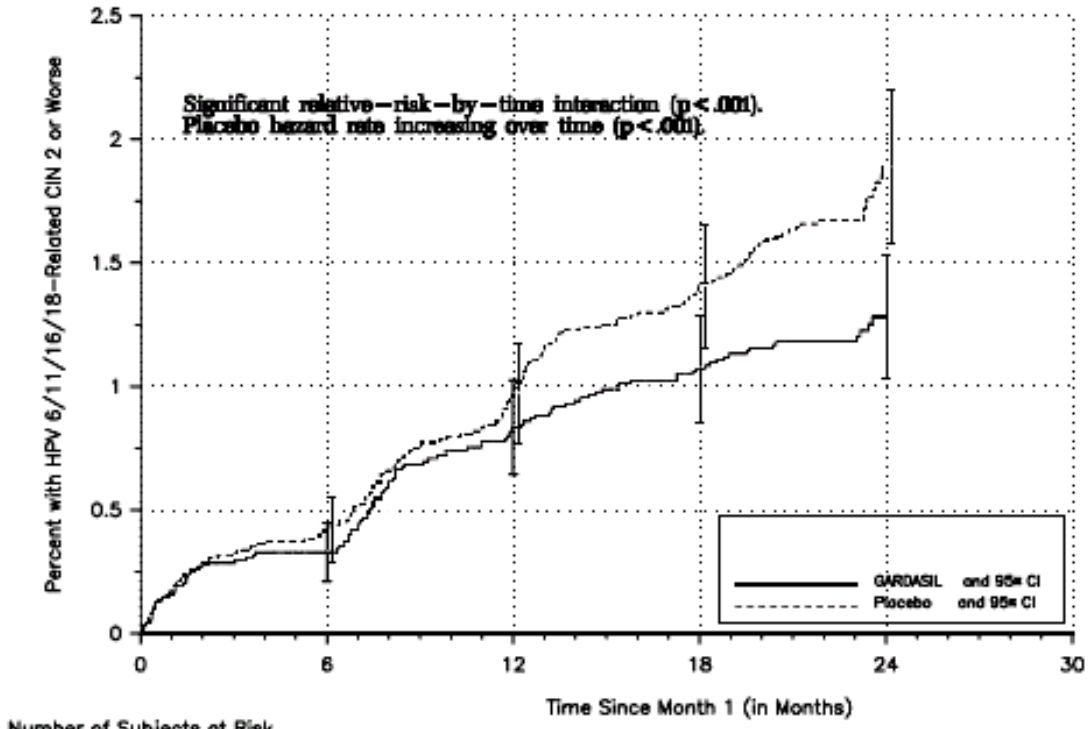
TABLE 257
Protocols 007, 013, 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related CIN 2/3 or Worse - PPE, MITT-2 and MITT-3 Population

	Gardasil N=9075				Placebo N=9075					
Study Population HPV 6/11/16/18 related CIN	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	7858	0	11887.6	0.0	7861	43	11888.4	0.4	**100.0%**	(91.0, 100%)
MITT-2, combined	8625	1	17139.1	0.0	8673	69	17231.2	0.4	**98.5%**	(91.6, 100.0%)
MITT-3, combined	8814	118	17467.0	0.7	8846	186	17527.5	1.1	**36.3%**	(19.4, 49.9%)

Source: Table 5.3.5.3.2:8, Integrated Summary of Efficacy, p. 43

- Time to event analysis for HPV 6, 11, 16, or 18 related CIN 2 or worse: Figure 29 below is a time to event analysis for HPV 6, 11, 16, or 18 related CIN 2 or worse. As time progresses, the number of subjects at risk decreases because not all subjects have been enrolled for the longer timepoints and because who developed disease are no longer available. The data suggest a lower risk of developing vaccine type HPV related CIN 2 or worse as time progresses. However, further follow-up is necessary before a definitive conclusion can be reached. Further data from the close-outs of Studies 013 and 015, as well as longer term follow-up of subjects enrolled in the extension phase of Study 015 is expected to provide additional information.

FIGURE 29
Protocols 007, 013, 015 Combined: Analysis of Time to HPV 6/11/16/18 Related CIN 2 or Worse – MITT-3 Population *(includes AIS)*



† A vaccine-HPV-type-related CIN is defined as a tissue sample diagnosed by the Pathology Panel as CIN or cervical cancer with vaccine-HPV-type DNA detected in tissue from the same lesion.
‡ Includes all subjects who received ≥1 vaccination. Cases were counted starting 30 days after Day 1. In Protocol 013, cervical biopsies that were performed in the absence of an abnormal Pap test result at the antecedent visit were excluded. In Protocol 015, cervical biopsies that were performed in the absence of an abnormal Pap test result at the antecedent visit were *included*.
CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; DNA = Deoxyribonucleic acid; HPV = Human papillomavirus; MITT = Modified intention to treat; Pap = Papanicolaou.

Source: Appendix 2.7.3-cervixcancer:71, p. 575, Summary of Clinical Efficacy-cervixcancer

Efficacy Against HPV 6, 11, 16, and/or 18 related CIN 1

The sponsor also provided an exploratory analysis against against HPV 6, 11, 16, and/or 18 related CIN 1. In these analyses efficacy was demonstrated in populations analyzed.

TABLE 258
Protocols 007, 013, and 015: Analysis of Efficacy of HPV 6, 11, 16, 18 related CIN 1 (PPE, MITT-2, and MITT-3 Populations)

Gardasil N=9075				Placebo N=9075					
n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE									
7858	4	11884.0	0.03	7861	58	11878.4	0.5	**93.1%**	(81.4, 98.2%)
MITT-2									
8625	8	17133.4	0.05	8673	106	17201.4	0.6	**92.4%**	(84.5, 96.8%)
MITT-3									
8814	97	17443.9	0.6	8846	213	17457.5	1.2	**54.4%**	(41.8, 64.5%)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n= number of subjects evaluable, i.e., the number of subjects in the given population who also have at least one follow-up visit.
Source: Table 5.3.5.3.2:8, Integrated Summary of Efficacy, p. 43-44

Efficacy Against HPV 6, 11, 16, and/or 18 related CIN

The sponsor provided an exploratory analysis of cases of all CIN due to any of the HPV types included in the vaccine (Studies 007, 013, and 015). There is evidence of efficacy in the PPE, MITT-2, and MITT-3 populations. However, when analysis is expanded to include cases in subjects seropositive and/or PCR positive at baseline (MITT-3), the estimate of efficacy decreases to 46.4% (95% CI: 35.2, 55.7%) as compared to the efficacy in the PPE and MITT-2 populations.

TABLE 259
Protocols 007, 013, 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN-PPE, MITT-2, and MITT- 3 Populations

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=9075				Placebo N=9075					
Study Population HPV 6/11/16/18 related CIN	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE, combined	7858	4	11884.0	0.03	7861	83	11873.9	0.7	**95.2%**	(87.2, 98.7%)
MITT-2, combined	8625	9	17133.4	0.1	8673	143	17193.8	0.8	**93.7%**	(87.7, 97.2%)
MITT-3, combined	8814	170	17418.8	1.0	8846	317	17425.9	1.8	**46.4%**	(35.2, 55.7%)

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects evaluable; i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Table 2.7.3-cervixcancer: 26, p. 121-2

Efficacy for Vaccine HPV Types, CIN

The vaccine efficacy against all CIN associated with HPV 6/11, HPV 16 or HPV 18 in the PPE, MITT-2, and MITT-3 populations efficacy estimates were highest in the PPE population and lowest in the MITT-3 population with naïve and non-naïve subjects. .

TABLE 260
Protocols 005, 007, 013, 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN by HPV Type- PPE, MITT-2, and MITT- 3 Populations

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=10572				Placebo N=10273					
Study Population HPV 6/11/16/18 related CIN	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE										
HPV 6/11	6897	0	10449.0	0.0	6827	23	10342.8	0.2	**100.0%**	(82.8, 100.0%)
HPV 16	7603	4	12907.9	0.0	7200	73	12197.1	0.6	**94.8%**	(86.2%, 98.6%)
HPV 18	7376	0	11179.1	0.0	7312	20	11079.5	0.2	**100.0%**	(79.9, 100.0%)
MITT-2, combined										
HPV 6/11	7649	2	15230.5	0.0	7693	39	15299.5	0.3	**94.8%**	(80.1, 99.4%)
HPV 16	8397	5	18224.5	0.0	8193	118	17683.4	0.7	**95.9%**	(90.1, 98.7%)
HPV 18	8145	2	16215.3	0.0	8204	35	16334.1	0.2	**94.2%**	(77.6, 99.3%)
MITT-3, combined										
HPV 6/11	8814	16	17486.7	0.1	8846	61	17532.0	0.3	**73.7%**	(53.8, 85.8%)
HPV 16*	10121	155	21696.4	0.7	9896	278	21153.3	1.3	**45.6%**	(33.6, 55.6%)
HPV 18*	8814	19	17486.3	0.1	8846	63	17539.5	0.4	**69.7%**	(48.8, 82.9%)

*N=number of subjects randomized to respective vaccination group who received at least 1 injection.
n=number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
*Analysis of HPV 16 related CIN or cancer includes the HPV 16 L1 VLP vaccine group in Studies 005 and 013 and Gardasil and placebo recipients in Protocols 007, 013, and 015. All other analyses exclude the HPV 16 L1 VLP vaccine group of Protocols 005 and013.
Source: Table 2.7.3-cervixcancer: 28, p. 126

Vaccine Efficacy by Severity of Lesions, CIN

An exploratory analysis of vaccine efficacy against HPV 6, 11, 16, 18 related CIN by severity of disease in the PPE and MITT-3 populations of combined studies 007, 013, and 015 is shown in Table 261. In the PPE population there is evidence of efficacy of Gardasil against all grades of CIN. Efficacy estimates in the MITT-3 population are reduced in comparison to those in the PPE population.

TABLE 261
Protocols 007, 013, 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related CIN by Severity of Disease –PPE and MITT 3 populations

	Gardasil N=9075				Placebo N=9075					
HPV 6/11/16/18 related CIN grade	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
PPE										
CIN 1	7858	4	11884.0	0.0	7861	58	11878.4	0.5	**93.1%**	(81.4, 98.2%)
CIN 2	7858	0	11887.6	0.0	7861	31	11889.6	0.3	**100%**	(87.4, 100%)
CIN 2 or Worse	7858	0	11887.6	0.0	7861	43	11889.4	0.4	**100%**	(91.0, 100%)
CIN 3 or worse	7858	0	11887.6	0.0	7861	26	11891.9	0.2	**100%**	(84.8, 100%
MITT-3										
CIN 1	8814	97	17443.9	0.6	8846	213	17457.5	1.2	**54.4%**	(41.8, 64.5%)
CIN 2	8814	73	17482.7	0.4	8846	124	17542.7	0.7	**40.9%**	(20.5, 56.4%)
CIN 2 or Worse	8814	118	17467.0	0.7	8846	186	17527.5	1.1	**36.3%**	(19.4, 49.9%)
CIN 3 or worse	8814	84	17478.8	0.5	8846	126	17551.4	0.7	**33.1%**	(11.1, 49.8%)

Subjects are counted once in each applicable category. A subject may appear in more than one category.
*N=number of subjects randomized to respective vaccination group who received at least 1 injection.
n=number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: From Table 27, p. 123-124, Summary of Efficacy- cervical lesions

External Genital Lesions

External genital lesions include condyloma acuminata, vulvar intraepithelial neoplasia (VIN) grades 1, and 2/3, and vaginal intraepithelial neoplaisa (VaIN) grades 1 and 2/3. The lesions that are of most clinical interest are the genital warts, VIN 2/3 and VaIN 2/3.

Efficacy Against HPV 6, 11, 16, or 18 related Condyloma Acuminata:

Analyses were conducted to evaluate vaccine efficacy against HPV 6, 11, 16, and 18 related condyloma. These analyses are shown for the PPE and MITT-3 populations. Efficacy was shown for condylomas caused by all HPV types in the PPE population, as well as the MITT-3 population. Most of these lesions were related to HPV 6 and 11. Most of these were vulvar condylomas, although several were vaginal in location.

TABLE 262
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related Condyloma by HPV type –PPE and MITT-3 Populations

	Gardasil N=9075				Placebo N=9075					
EGL Type	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE Population										
HPV 6, 11, 16 , 18 condyloma	7897	1	11977.9	0.0	7899	91	11953.4	0.8	98.9%	(93.7, 100.0%)
HPV 6	6930	1	10512.0	**0.0**	6856	74	10395.7	**0.7**	**98.7%**	**(92.3, 100.0%)**
HPV 11	6930	0	10513.3	**0.0**	6856	17	10418.0	**0.2**	**100.0%**	**(76.0, 100.0%)**
HPV 16	6647	0	10089.6	**0.0**	6463	14	9810.7	**0.1**	**100.0%**	**(70.7, 100.0%)**
HPV 18	7411	0	11243.0	**0.0**	7340	7	11156.7	**0.1**	**100.0%**	**(31.2, 100.0%)**
MITT-3 population										
HPV 6, 11, 16, 18 related condyloma	8954	58	17068.3	**0.3**	8962	184	17593.1	**1.0**	**68.5%**	**(57.5, 77.0%)**
HPV 6	8954	53	17616.4	**0.3**	8962	154	17619.2	**0.9**	**65.6%**	**(52.7, 75.3%)**
HPV 11	8954	4	17673.6	**0.0**	8962	31	17714.8	**0.2**	**87.1%**	**(63.4, 96.7%)**
HPV 16	8954	3	17675.7	**0.0**	8962	21	17725.3	**0.1**	**85.7%**	**(52.0, 97.3%)**
HPV 18	8954	1	17677.9	**0.0**	8962	15	17727.4	**0.1**	**93.3%**	**(56.5, 99.8%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection. n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Amendment 34, Tables 1-1 and 1-3, Efficacy Information Amendment, 5/17/06

Efficacy Against HPV 6, 11, 16, or 18 related VIN 2/3 or VaIN 2/3: This endpoint was included in a co-primary composite endpoint in Study 013, and evaluated in combined analyses of 007, 013, and 015.

Vulvar lesions may or may not be associated with HPV. In older women, they are less likely to be associated with HPV infection, and in younger women there is more likely to be an association. The incidence of VIN has increased in younger women during the 1970's through 1990's.[7,8,9] VIN 3 is the most common presentation for VIN lesions and is thought to be a precursor lesion for invasive vulvar cancer caused by HPV.[10] In the

[7] Joura EA. Current Opinion in Obstetrics and Gynecology 2002;14:39-43
[8] Canavan TP and Cohen D. American Family Physician 2002; 66(7): 1269-74
[9] Al-Ghamdi A et al. Gynecologic Oncology 2002; 84: 94-101
[10] Herod JJ et al. British Journal Obstetrics and Gynaecology 1996; 103 (5): 446-52.

clinicopathologic study by Al-Ghamdi et al, the authors noted that the incidence of vulvar invasive squamous cell carcinoma has increased over time (1970-1998). Most of these tumors in the younger study population were associated with HPV. VaIN is often seen in women with cervical dysplasia[11], and in one study, 27/71 cases of VaIN occurred in subjects with previous or concomitant CIN.[12]

TABLE 263
Protocols 007, 013, and 015 Combined: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VIN 2/3 or VaIN 2/3 or worse (PPE, MITT-2, and MITT-3 Populations)

	Gardasil N=9075				Placebo N=9075					
Study Population	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
Per Protocol										
VIN 2/3 or VaIN 2/3 or worse	7897	0	11979.2	**0.0**	7899	13	11986.9	**0.1**	**100.0%**	**(67.2, 100.0%)**
MITT -2										
VIN 2/3 or VaIN 2/3 or worse	8760	0	17309.4	**0.0**	8786	26	17391.9	**0.1**	**100.0%**	**(84.7, 100.0%)**
MITT-3										
VIN 2/3 or VaIN 2/3 or worse	8954	8	17672.3	**0.0**	8962	30	17722.6	**0.2**	**73.3%**	**(40.3, 89.4%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
N = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of Efficacy external genital lesions, 2.7.3:Appendix 8, p. 63

The sponsor also provided a combined analysis of efficacy against HPV 16/18 related VIN 2/3 or VaIN 2/3 or worse. The results are shown in Table 264 below.

[11] Daling JR et al. Gynecologic Oncology 2002; 84: 263-70.
[12] Sugase M and Matsukuru T. International Journal of Cancer 1997; 72 (3): 412-5.

TABLE 264
Protocols 007, 013, and 015 Combined: Analysis of Efficacy Against HPV 16/18 Related VIN 2/3 or VaIN 2/3 or worse (PPE, MITT-2, and MITT-3 Populations)

	Gardasil N=9075				Placebo N=9075					
Study Population	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
Per Protocol										
VIN 2/3 or VaIN 2/3 or worse	7769	0	11786.6	0.0	7741	10	11752.8	0.1	100%	(55.5, 100.0%)
MITT -2										
VIN 2/3 or VaIN 2/3 or worse	8641	0	17079.0	0.0	8667	24	17160.9	0.1	100%	(83.3, 100.0%)
MITT-3										
VIN 2/3 or VaIN 2/3 or worse	8954	8	17672.3	0.0	8962	26	17726.0	0.1	69.1%	(29.8, 87.9%)

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of Efficacy external genital lesions, 2.7.3:Table 7, p. 41

Efficacy Against HPV 6, 11, 16, or 18 related VIN 2/3

- Although there are few cases of vaccine HPV type VIN 2/3 efficacy in the PPE population is 100% (95% CI: 41.4, 100.0%). Most of the VIN 2/3 lesions were associated with HPV 16.

TABLE 265
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VIN 2/3: PPE and MITT-3 Populations

	Gardasil N=9075				Placebo N=9075					
HPV 6, 11, 16, 18 related VIN 2/3	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE	7897	0	11979.2	**0.0**	7899	8	11988.3	**0.1**	**100.0%**	**(41.4, 100.0%)**
MITT-3	8954	7	17673.1	**0.0**	8962	22	17726.6	**0.1**	**68.1%**	**(22.7, 88.5%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Amendment 34, Table 1-1 and 1-3, Efficacy Information Amendment, 5/17/06

Efficacy Against HPV 6, 11, 16, or 18 related VaIN 2/3

There were few cases of vaccine HPV type VaIN 2/3. Although the lower bound on the 95% CI is less than zero in the PPE and MITT-3 population analyses, the case split is

favorable in both populations. The VaIN 2/3 lesions were more often related to HPV 16 and 18 as compared to HPV 6 and 11.

TABLE 266
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 related VaIN 2/3 – PPE and MITT-3 Populations

	Gardasil N=9075				Placebo N=9075					
Population	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE	7897	0	11979.2	**0.0**	7899	5	11989.9	**0.04**	**100.0%**	**(<0.0, 100.0%)**
MITT-3	8954	2	17678.4	**0.01**	8962	9	17734.5	**0.1**	**77.7%**	**(<0.0, 97.7%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Amendment 34, Tables 1-1 and 1-3, Efficacy Information Amendment, 5/17/06

Efficacy against HPV 6, 11, 16, and/or 18 related VIN 1
Few cases of VIN 1 were detected in the studies. In the combined exploratory analyses of the PPE population, there is evidence of efficacy against vaccine type HPV related VIN 1. In the MITT-3 population, there is a trend towards efficacy, but this does not reach statistical significance.

TABLE 267
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VIN 1: PPE and MITT-3 Populations

Gardasil N=9075				Placebo N=9075					
n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE									
7987	0	11979.2	**0.0**	7899	10	11986.3	**0.1**	**100%**	**(41.9, 100%)**
MITT-3									
8954	8	17673.0	**0.05**	8962	19	17725.6	**0.1**	**57.8%**	**(<0.0, 84.0%)**

Source: Tables 1-1 and 1-3, Efficacy Information Amendment, 5/17/06, p. 3 and 7

Efficacy against HPV 6, 11, 16, and/or 18 related VaIN 1

- The exploratory analyses of efficacy against VaIN 1 in the PPE and MITT-3 populations suggest evidence of efficacy.

TABLE 268
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related VaIN 1: PPE and MITT-3 Populations

Gardasil N=9075				Placebo N=9075					
n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
PPE									
7987	0	11979.2	**0.0**	7899	7	11987.5	**0.1**	**100%**	**(30.6, 100%)**
MITT-3									
8954	4	17674.4	**0.02**	8962	17	17725.6	**0.1**	**76.4%**	**(27.7, 94.2%)**

Source: Tables 1-1 and 1-3, Efficacy Information Amendment, 5/17/06, p. 4 and 8

Efficacy Against HPV 6, 11, 16, and/or 18 related EGLs

Efficacy against HPV 6, 11, 16, and/or 18 related external genital lesions in the PPE, MITT-2 and MITT-3 populations for combined analyses of Protocols 007, 013, and 015 are shown in Table 269 below. Efficacy estimates are highest for analyses of naïve populations (PPE and MITT-2). When naïve and non-naïve subjects are included in the analysis population the estimate of efficacy decreased to 70.4% (95% CI: 61.0, 77.7%).

TABLE 269
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6/11/16/18 related EGLs

	Gardasil N=9075				Placebo N=9075					
Study Population	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	**95% CI**
Per Protocol										
Combined Porotocols	7987	1	11977.9	**0.0**	7899	113	11943.2	**0.9**	**99.1%**	**(95.0, 100.0%)**
MITT -2										
Combined Protocols	8760	9	17300.4	**0.1**	8786	174	17297.5	**1.0**	**94.8%**	**(90.0, 97.7%)**
MITT-3										
Combined Protocols	8954	68	17595.0	**0.4**	8962	229	17560.1	**1.3**	**70.4%**	**(61.0, 77.7%)**

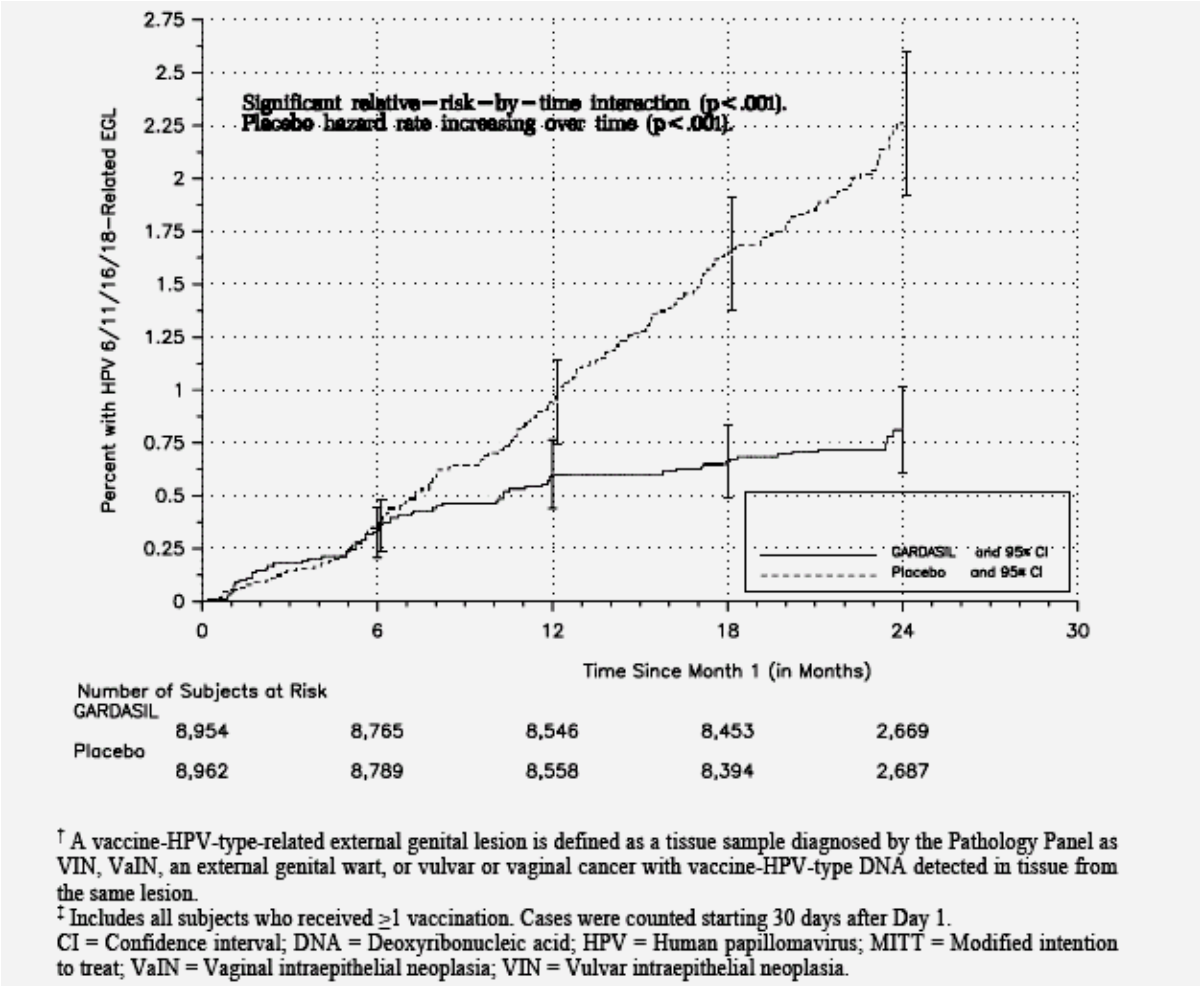
N= N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of external genital lesions, Table 2.7.3: 6, p 39-40

Time to event analysis for HPV 6, 11, 16, and/or 18 related EGL

Figure 30 below shows an analysis to time event for cases of HPV 6, 11, 16, and/or 18 related EGLs in the MITT-3 population. As subjects are followed the number of cases in the placebo group increases relative to the number of cases in the vaccinated group raising the possibility that Gardasil does not prevent EGL disease related to vaccine type

HPV infection present at the time of vaccination, although there may be benefit for vaccine type EGL disease related to infection that occurs after vaccination.

FIGURE 30
Protocols 007, 013, 015 Combined: Analysis of Time to HPV 6/11/16/18 Related EGL – MITT-3 Population



† A vaccine-HPV-type-related external genital lesion is defined as a tissue sample diagnosed by the Pathology Panel as VIN, VaIN, an external genital wart, or vulvar or vaginal cancer with vaccine-HPV-type DNA detected in tissue from the same lesion.
‡ Includes all subjects who received ≥1 vaccination. Cases were counted starting 30 days after Day 1.
CI = Confidence interval; DNA = Deoxyribonucleic acid; HPV = Human papillomavirus; MITT = Modified intention to treat; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Source: Summary of efficacy - external genital lesions, Appendix 2.7.3:10, p. 65

Efficacy Against HPV 6, 11, 16, and/or 18 related EGLs by HPV type
Estimates of efficacy against EGLs associated with HPV type 6/11, 16, and 18 in the PPE, MITT-2, and MITT-3 populations were provided by the sponsor. Efficacy was demonstrated for all endpoints. Most cases of EGLs were associated with HPV 6/11 vaccine types. Subjects in studies 013 and 015 were excluded if they had a history of genital warts or genital warts at day 0, and subjects in study 007 were excluded if they had a history of, or history of treatment for genital warts. Thus, there may be fewer subjects with EGLs related to vaccine HPV types included in the overall population because they would have been excluded prior to entry. This may account in part for the

higher estimate of efficacy against vaccine HPV related EGLs in the MITT-3 population for EGLs as compared to the estimate of efficacy seen in the same population for CIN.

TABLE 270
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6/11, 16, 18 related EGL by HPV Type – PPE, MITT-2 and MITT-3 Populations

	Gardasil N=9075				Placebo N=9075					
Study Population HPV type related EGL	N	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	Nes 1	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
Per Protocol										
HPV 6/11	6930	1	10512.0	**0.0**	6856	97	10384.1	**0.9**	**99.0%**	**(94.2, 100.0%)**
HPV 16	6647	0	10089.6	**0.0**	6463	26	9807.6	**0.3**	**100.0%**	**(85.2, 100.0%)**
HPV 18	7411	0	11243.0	**0.0**	7340	9	11154.8	**0.1**	**100.0%**	**(49.7, 100.0%)**
MITT -2										
HPV 6/11	7769	8	15359.6	**0.1**	7789	143	15366.9	**0.9**	**94.4%**	**(88.7, 97.6%)**
HPV 16	7438	1	14707.0	**0.0**	7441	45	14722.9	**0.3**	**97.8%**	**(87.0, 99.9%)**
HPV 18	8272	0	16351.3	**0.0**	8311	17	16462.0	**0.1**	**100.0%**	**(75.6, 100.0%)**
MITT-3										
HPV 6/11	8954	59	17607.5	**0.3**	8962	194	17586.1	**1.1**	**69.6%**	**(59.2, 77.7%)**
HPV 16	8954	11	17664.8	**0.1**	8962	55	17705.2	**0.3**	**80.0%**	**(61.3, 90.5%)**
HPV 18	8954	2	17676.5	**0.0**	8962	20	17723.7	**0.1**	**90.0%**	**58.7, 98.9%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of Efficacy-External Genital lesions: Appendix 2.7.3: 9, p. 64

Vaccine Efficacy by Severity of Lesions, EGLs

Efficacy against HPV 6, 11, 16, and 18 related EGLs by severity is presented in Table 271. In these analyses cases of VIN 1 or VaIN 1 and VIN 2/3 or VaIN 2/3 are presented separately. As noted previously, efficacy in the MITT-3 population appears to be lower than that assessed in naïve subjects (PPE and MITT-2 populations).

TABLE 271
Protocols 007, 013, and 015 Combined: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related EGL by Severity of Disease

	Gardasil N=9075				Placebo N=9075					
Study Population	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
Per Protocol										
Condyloma, VIN 1 or VaIN 1	7897	1	11977.9	**0.0**	7899	102	11946.4	**0.9**	**99.0%**	**(94.4, 100.0%)**
VIN 2/3 or VaIN 2/3 or worse	7897	0	11979.2	**0.0**	7899	13	11986.9	**0.1**	**100.0%**	**(67.2, 100.0%)**
MITT -2										
Condyloma, VIN 1 or VaIN 1	8760	9	17300.4	**0.1**	8786	155	17306.4	**0.9**	**94.2%**	**(88.7, 97.4%)**
VIN 2/3 or VaIN 2/3 or worse	8760	0	17309.4	**0.0**	8786	26	17391.9	**0.1**	**100.0%**	**(84.7, 100.0%)**
MITT-3										
Condyloma, VIN 1 or VaIN 1	8954	62	17602.3	**0.4**	8962	207	17572.9	**1.2**	**70.1%**	**(60.1, 77.9%)**
VIN 2/3 or VaIN 2/3 or worse	8954	8	17672.3	**0.0**	8962	30	17722.6	**0.2**	**73.3%**	**(40.3, 89.4%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of Efficacy external genital lesions, 2.7.3:Appendix 8, p. 63

CIN and EGL irrespective of HPV type

Gardasil includes four HPV types and is not expected to be effective against endpoints not associated with vaccine HPV types. In the individual study reports the sponsor provided data to address whether Gardasil has any efficacy against disease not associated with vaccine HPV types. This analysis was not provided for the combined studies. However, to address whether there is any population benefit against CIN or EGL irrespective of HPV type the sponsor has provided analyses of the efficacy of Gardasil against CIN and EGLs irrespective of HPV type (i.e. due to vaccine types and not due to vaccine types). These analyses are provided in the following tables and figures. Testing for non-vaccine HPV types present in CIN and EGL lesions was not provided in the BLA but is expected to be submitted by the sponsor in 2007.

Efficacy against any CIN or worse, CIN 2 or worse, CIN 3 or worse irrespective of HPV type

Table 272 below shows the efficacy of Gardasil against CIN for the RMITT-2, RMITT-3, and MITT-3 populations. Although the Pap test has limited sensitivity the RMITT-2 population (subjects with normal Pap who are seronegative and PCR negative to vaccine types at baseline) may be the analysis population which best represents a group of subjects which do not have HPV associated disease at baseline. Efficacy estimates using the RMITT-2 population are higher than those using the RMITT-3 population (subjects naïve and non-naïve to vaccine HPV types with normal and abnormal Pap test at baseline) populations. There appear to be little benefit in the MITT-3 population, although when the MITT-3 subjects have a normal Pap test at baseline (RMITT-3), the point estimates of efficacy are slightly higher (although most without statistical significance).

TABLE 272
Protocols 007, 013, and 015 Combined: Impact of GARDASIL on the Incidence of CIN Irrespective of HPV Type by Severity of Disease

	Gardasil N=9075				Placebo N=9075					
Study Population CIN Grade	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	**Percent Reduction**	95% CI
Restricted MITT-2										
CIN 1 or worse	5638	222	11238.7	2.0	5701	286	11313.1	2.5	**21.9%**	(6.6, 34.7%)
CIN 2 or worse	5638	59	11333.4	0.5	5701	96	11454.4	0.8	**37.9%**	(13.2, 55.9%)
CIN 3 or worse	5638	28	11344.4	0.2	5701	52	11474.5	0.5	**45.5%**	(12.2, 66.9%)
Restricted MITT-3										
CIN 1 or worse	7457	371	1478.8	**2.5**	7481	460	14753.3	**3.1**	**19.5%**	**(7.5, 30.0%)**
CIN 2 or worse	7457	134	14923.1	**0.9**	7481	171	14967.6	**1.1**	**21.4%**	**(0.9, 37.8%)**
CIN 3 or worse	7457	74	14941.9	**0.5**	7481	100	14997.7	**0.7**	**25.7%**	**(<0.0, 45.8%)**
MITT-3										
CIN 1 or worse	8814	677	17089.2	4.0	8846	784	17079.7	4.6	**13.7%**	(4.2, 22.2%)
CIN 2 or worse	8814	287	17409.5	1.6	8846	328	17469.4	1.9	**12.2%**	(<0.0, 25.3%)
CIN 3 or worse	8814	168	17460.9	1.0	8846	190	17532.7	1.1	**11.2%**	(<0.0, 28.3%)

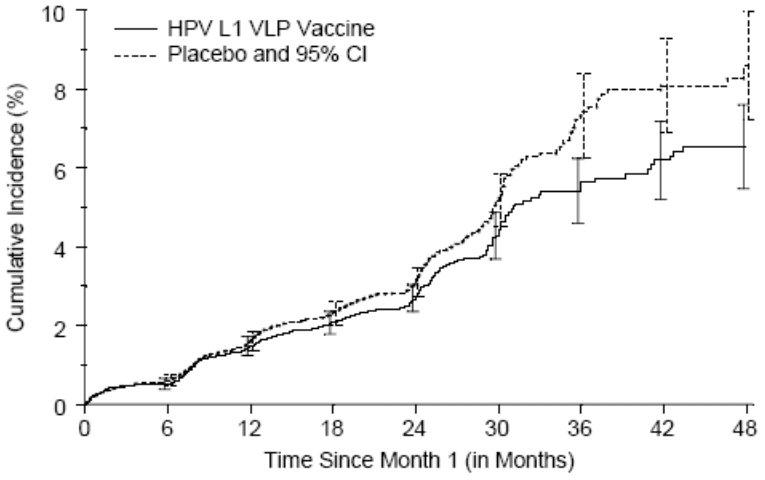
Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects evaluable, i.e., number of subjects in the given population who have at least one follow-up visit.
Source: Integrated Summary of Efficacy, Table 5.3.5.3.2: 17, p. 78-9

Time to event for CIN 2 or worse

A time to event curve for the diagnosis of CIN 2 or worse irrespective of HPV type in combined studies 005, 007, 013, and 015 was provided. The sponsor reports that the

Gardasil group may have a lower incidence of CIN 2 irrespective of HPV type as time progresses, although the 95% CIs do overlap. Additional data, expected from Studies 013 and 015, may address whether there is a lower incidence of CIN 2 due to any HPV type in Gardasil recipients.

FIGURE 31
Protocols 005, 007, 013, 015: Plot of Time to Diagnosis of CIN 2 or worse Irrespective of HPV Type – MITT-3 Population



	Number of Subjects at Risk								
HPV L1 VLP Vaccine	9831	9705	9365	9178	3790	1363	897	813	276
Placebo	9896	9764	9431	9213	3902	1388	869	793	246

† A CIN due to any HPV type is defined as a tissue sample diagnosed by the Pathology Panel as CIN. Biopsies outside the context of the study were included. In Protocols 013 and 015, cervical biopsies that were performed in the absence of an abnormal Pap test result at the antecedent visit were *included*.
‡ Includes all subjects who received ≥1 vaccination. Cases were counted starting 30 days after Day 1. The HPV L1 VLP Vaccine group includes subjects who received either the monovalent HPV 16 vaccine or the quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine. The monovalent HPV 16 vaccine group of Protocol 013 was excluded from the analysis.

Source: Amendment 0027, Figure from response to additional CBER questions to MRL (5/2/06)

Efficacy against EGL irrespective of HPV type
There is evidence of vaccine efficacy EGLs in the population analyzed.

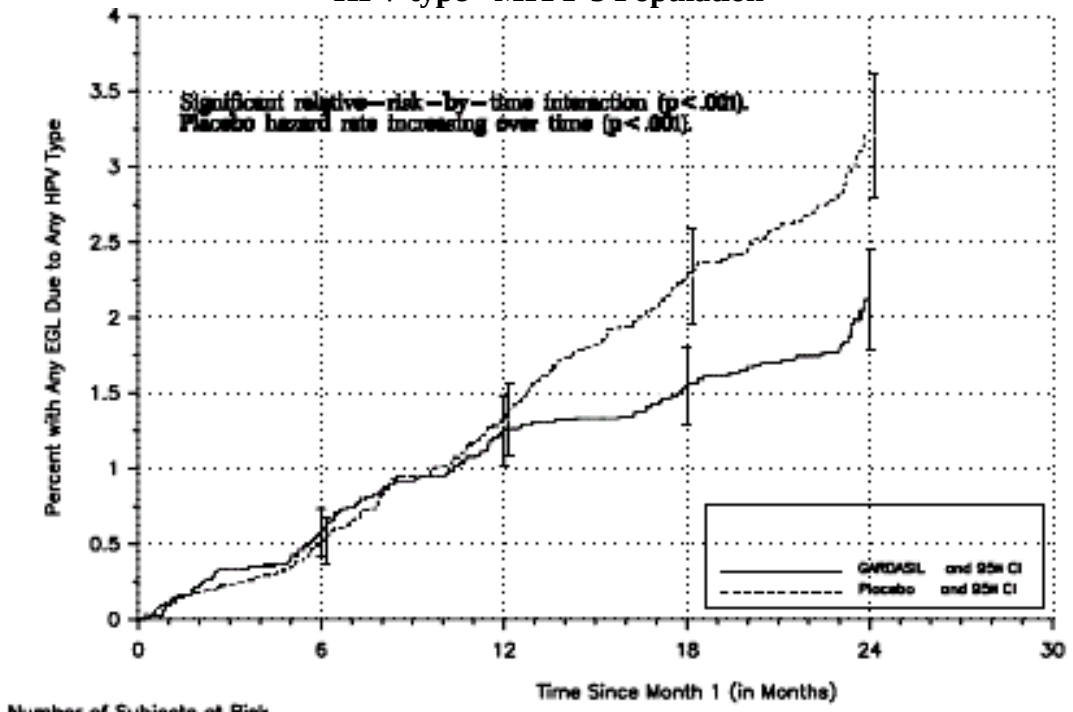
TABLE 273
Protocols 007, 013 and 015: Impact of Gardasil on the Incidence of EGLs Irrespective of HPV Type by Severity of Disease-RMITT-2 and MITT-3 Populations

	Gardasil N=9075				Placebo N=9075					
Study Population EGL Type	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
RMITT-2										
Any EGL	5734	57	11298.0	**0.5**	5769	167	11345.6	**1.5**	**65.7%**	**(53.4, 75.1%)**
Condyloma, VIN 1 or VaIN 1	5734	52	11300.0	**0.5**	5769	151	11353.8	**1.3**	**65.4%**	**(52.3, 75.3%)**
VIN 2/3 or VaIN 2/3 or worse	5734	5	11339.3	**0.0**	5769	27	11439.9	**0.2**	**81.3%**	**(50.8, 94.4%)**
MITT-3										
Any EGL	8954	185	17487.4	**1.1**	8962	307	17480.0	**1.8**	**39.8%**	**(27.5, 50.1%)**
Condyloma, VIN 1 or VaIN 1	8954	169	17499.4	**1.0**	8962	284	17497.4	**1.6**	**40.5%**	**(27.8, 51.1%)**
VIN 2/3 or VaIN 2/3 or worse	8954	22	17665.0	**0.1**	8962	43	17709.5	**0.2**	**48.7%**	**(12.3, 70.8%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Summary of efficacy-external genital lesions – Table 2.7.3:9, p. 46

Time to event for EGLs irrespective of HPV type. The time to any EGL irrespective of HPV type is shown below, and suggests that there may be increased benefit to Gardasil recipients in the MITT-3 population as time progresses (see Figure 32 below).

FIGURE 32
Protocols 007, 013, 015 Combined: Analysis of Time to Any EGL Irrespective of HPV type - MITT-3 Population



Number of Subjects at Risk					
GARDASIL	8,954	8,743	8,489	8,377	2,633
Placebo	8,962	8,775	8,525	8,339	2,648

[1] An external genital lesion is defined as a tissue sample diagnosed by the Pathology Panel as VIN, VaIN, or external genital wart. Biopsies outside the context of the study were included.
[2] Includes all subjects who received ≥1 vaccination. Cases were counted starting 30 days after Day 1.
CI = Confidence interval; EGL = External genital lesions; HPV = Human papillomavirus; MITT = Modified intention to treat; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.
Source: Summary of efficacy-external genital lesions, Appendix 2.7.3: 12, p. 67

Efficacy against VIN 2/3 and VaIN irrespective of HPV type

The sponsor provided an analysis of efficacy in the MITT-3 population against VIN 2/3 and VaIN 2/3 irrespective of HPV (see Table 274 below). Although there were more cases of VIN 2/3 and VaIN 2/3 in the placebo group the efficacy estimates are very wide, thus it is difficult to draw definitive conclusions.

TABLE 274
Protocols 007, 013, and 015: Analysis of Efficacy Against
VIN 2/3 and VaIN2/3 Irrespective of HPV Type – MITT-3 Population

	Gardasil N=9075				Placebo N=9075					
EGL Type	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
VIN 2/3	8954	14	17667.2	**0.1**	8962	28	17722.1	0.2	**49.8%**	**(1.5, 75.6%)**
VaIN 2/3	8954	8	17677.0	**0.05**	8962	16	17725.9	**0.1**	**49.9%**	**(<0.0, 81.4%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
Source: Amendment 34, Tables 1-5, Efficacy Information Amendment, 5/17/06

Vaccine Efficacy in Non-Naïve Subjects

During the efficacy review of study 013 a concern was raised for disease enhancement in a subgroup analysis of subjects who had evidence of persistent infection with vaccine-relevant HPV types at baseline. The sponsor therefore provided combined studies analyses of efficacy of Gardasil against CIN and EGL in subgroups of subjects non-naïve at baseline as follows:

Seropositive and PCR Negative at Baseline
Seronegative and PCR Positive at Baseline
Seropositive and PCR Positive at Baseline

Of note these analyses were exploratory, and were subgroup analyses, and thus interpretation of the data

HPV 16/18 related CIN 2/3, AIS or worse

In the combined studies analysis of efficacy of Gardasil against HPV 16/18 related CIN 2/3 in the MITT-3 population, efficacy was reduced (39.0%, 95% CI: 23.3, 51.7%) as compared to analyses which included only naïve subjects (PCR negative and seronegative). Exploratory subgroup analyses of efficacy in subjects included in the MITT-3 population based on their baseline PCR and seropositivity status had been provided to further evaluate potential therapeutic potential of the vaccine. Additional analyses were requested by CBER and provided by the sponsor to further evaluate the potential for disease enhancement in view of the findings in the seropositive and PCR positive subgroup from study 013. In subjects non-naïve at baselne – with either evidence of previous infection (seropositive) or baseline infection (PCR positive), the efficacy estimates are wide and the lower bound of the 95% CI less than zero. In the subgroup of subjects seropositive and PCR positive at baseline, efficacy is -25.8% (95% CI: -76.4, 10.1%).

TABLE 275
Protocols 005, 007, 013, 015: Efficacy Against HPV 16/18 related CIN 2/3, AIS or Worse – MITT-3 Population, by Initially Baseline HPV Status

	Gardasil N=10268			Placebo N=10273			
Day 1 Status	n*	No. of cases	Incidence Rate/100 person years at risk	n*	No. of cases	Incidence rate/100 person years at risk	**Vaccine Efficacy 95% CI**
MITT-3	9831	122	0.6	9896	201	0.9	**39.0% (23.3, 51.7%)**
PCR (-) Sero (-)	9342	1	0.0	9400	81	0.4	**98.8% (92.9, 100.0%)**
PCR (-) Sero (+)	853	0	0.0	910	4	0.2	**100.0% (-63.6, 100.0%)**
PCR (+) Sero (-)	661	42	3.2	626	57	4.6	**31.2% (-4.5, 54.9%)**
PCR (+) Sero (+)	473	79	9.1	499	69	7.3	**-25.8% (-76.4, 10.1%)**
Sero and/or PCR (+)		[121]			[130]		**(No efficacy estimate provided)**

*Some subjects are counted in more than one row due to different baseline PCR/serostatus for HPV 16 and HPV 18. Each subject is counted once within each applicable row for HPV 16 or HPV 18.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable.
[ ] = total number of cases where subjects are PCR + and/or sero+ in the respective group
Source: Amendment 0024, Table 1-1, efficacy information amendment submitted 4/24/06

HPV 6/11/16/18 related CIN and CIN 2 or worse

Table 276 presents subgroup analyses of efficacy against HPV 6/11/16 or 18 related CIN in subjects non-naïve (PCR positive and/or seronegative) at baseline and show low point estimates for efficacy with negative lower bounds. This population is a composite of subpopulations (PCR positive and seropositive, PCR positive and seronegative, and PCR negative and seropositive to one or more vaccine HPV types). Thus, subjects in this composite population will be counted once. However, in the tables presenting efficacy in subpopulations by baseline characteristics, subjects may be counted more than once depending on baseline characteristics to individual HPV vaccine types.

TABLE 276
Protocols 007, 013 and 015: Analysis of Efficacy Against Vaccine HPV Type Related CIN Among Subjects who were PCR Positive and/or Seropositive for the Relevant HPV Type at Day 1

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=9075				Placebo N=9075					
Endpoint	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	2322	163	4397.9	**3.7**	2323	183	4387.5	4.2	**11.1%**	**(<0.0, 28.5%)**
HPV 6/11/16/18 related CIN 2 or worse	2322	117	4440.5	**2.6**	2323	123	4452.6	**2.8**	**4.6%**	**(<0.0, 26.6%)**

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Table 1e-4, Amendment 0019 to BLA, Additional Efficacy Analyses Requested by CBER, 4/7/06.

When efficacy is assessed in the subgroup of non-naïve subjects, those PCR positive and seronegative for the vaccine HPV types, efficacy estimates are shown below.

TABLE 277
Protocols 007, 013, 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN Among Subjects who were PCR Positive and Seronegative for the Relevant HPV Type(s) at Day 1

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=9075				Placebo N=9075					
Endpoint	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	798	70	1491.0	**4.7**	767	91	1424.6	6.4	**26.5%**	**(<0.0, 47.0%)**
HPV 6/11/16/18 related CIN 2 or worse	798	42	1517.0	**2.8**	767	56	1462.5	**3.8**	**27.7%**	**(<0.0, 52.7%)**

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0015, Efficacy Information Amendment, 3/22/06, submitted in response to CBER questions 3/1/06, Table 2d-3, p. 34

When efficacy is assessed in another subgroup of non-naïve subjects, those PCR negative and seropositive at baseline, there are fewer cases in both subjects administered Gardasil or placebo relative to the number of cases observed in PCR positive subjects. This subgroup may represent subjects who have successfully cleared prior infections due to vaccine serotypes and ***may*** have fewer newly diagnosed cases of CIN due to vaccine HPV types.

TABLE 278
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6/11/16/18 Related CIN Among Subjects who were PCR Negative and Seropositive for the Relevant HPV Type(s) at Day 1

	20/40/40/20 HPV 6, 11, 16, 18 vaccine N=9075				Placebo N=9075					
Endpoint	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	1245	0	2454.1	**0.0**	1283	5	2528.6	0.2	**100.0%**	**(<0.0, 100.0%)**
HPV 6/11/16/18 related CIN 2 or worse	1245	0	2454.1	**0.0**	1283	3	2529.1	**0.1**	**100.0%**	**(<0.0, 100%)**

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
N=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Amendment 0015, Efficacy Information Amendment, 3/22/06, submitted in response to CBER questions 3/1/06, Table 2d-8, p. 38

In the subjects who were **seropositive and PCR positive at baseline,** there was a trend towards a negative effect of the vaccine on the incidence of CIN 2/3 or worse related to vaccine HPV types with which they were previously exposed. However, none of point estimates reached statistical significance.

TABLE 279
Protocols 007, 013, and 015: Analysis of Efficacy Against HPV 6/11/16/18-Related CIN or AIS Among Subjects Who Were Seropositive <u>and</u> PCR Positive for the Relevant HPV Type at Day 1

	Gardasil N=9075				Placebo N=9075					
Endpoint	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 related CIN	568	94	999.6	**9.4**	580	94	1016.3	**9.2**	**-1.7%**	**(<0.0, 24.4%)**
HPV 6/11/16/18 related CIN 2 or worse	568	75	1016.2	**7.4**	580	69	1044.0	**6.6**	**-11.7%**	**(<0.0, 20.6%)**

N=number of subjects randomized to the respective vaccination group who received at least 1 injection.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Efficacy Information Amendment, 4/7/06, Table 1b-1, p. 4.

An exploratory subgroup analysis of Study 013 subjects PCR positive and seropositive at baseline had raised concerns for potential disease enhancement among such subjects (observed efficacy against HPV 6/11/16/18 CIN 2/3 or worse -33.7% [95% CI: <0.0, -15.3%]). A similar subgroup analysis of subjects enrolled in Study 015, while not elminating the concern, provided some level of assurance (observed efficacy 5.4% [95% CI: <0.0, 39.0%]). To evaluate this further, the review team requested baseline characteristics of 013 and 015 subjects who were initially seropositive and PCR positive (in study 007, two subjects administered Gardasil and teo administered placebo were PCR positive and seropositive at baseline). These data are summarized in Tables 280 and 281.

The sponsor noted that in Study 013, the seropositive and PCR positive population represented a slightly larger proportion of the group that received Gardasil (5.7%) compared with the placebo group (5.0%). The inverse was seen in Study 015.

In addition, in Study 013, there was a higher proportion of subjects who developed CIN 2/3 within the seropositive and PCR positive Gardasil group (19.9%) as compared to the placebo group (13.9%). The proportions of subjects within the seropositive and PCR positive population with a CIN 2/3 case were comparable among the groups that received placebo in Protocol 013, placebo in Protocol 015, and Gardasil in Protocol 015.

TABLE 280
Size of Seropositive and PCR Positive Population Compared with the General Population of Protocol 013, Protocol 015, and the Database for Protocol 013 and 015 Combined

Day 1 Parameter	Gardasil			Placebo		
	013	015	013+015	013	015	013+015
S+/P+ population as percentage of study population	156/2723 (5.7%)	398/6087 (6.5%)	554/8810 (6.3%)	137/2732 (5.0%)	430/6080 (7.1%)	567/8812 (6.4%)
Subjects with CIN 2/3 as percentage of S+/P+ population	31/156 19.9%	42/398 10.6%	73/554 13.2%	19/137 13.9%	48/430 11.2%	67/567 11.8%

Source: Table 2a-1, Efficacy Information Amendmentm 3/22/06, p. 23

An imbalance in the percentage of subjects with a baseline Pap test of HSIL was also noted in Study 013 between the Gardasil (6.5%) and placebo (3.7%) groups. There was a smaller difference between the treatment groups in Study 015 (4.4% in the Gardasil group and 3.7% in the placebo group). For Studies 013 and 015 combined, of the 554 Gardasil recipients who were seropositive and PCR positive at baseline, 5.0% had HSIL at baseline as compared to 3.7% of placebo recipients. (See Table 281 below.)

TABLE 281
Protocols 013 and 015: Percentage of subjects with HSIL at Day 1 in subjects who were Seropositive and PCR Positive at Day 1

Day 1 Parameter	Gardasil			Placebo		
	013 N=156	015 N=398	013+015 N=554	013 N=137	015 N=430	013+015 N=567
Percantage of subjects wih a satisfactory Pap test with HSIL	6.5%	4.4%	5.0%	3.7%	3.7%	3.7%

Source: Table 2a-2, Efficacy Information Amendment 3/22/06, p. 24

Despite some statistical difficulty in interpreting subgroup data, the sponsor conducted a logistic regression analysis in which the probability of developing a case if HPV 6/11/16/18 related CIN 2 or worse was modeled as a function of the following characteristics: smoking status, region, age, lifetime number of sexual partners, number of new sexual partners in the 6 months prior to study start, and Pap test diagnosis, using logistic regression. Vaccination group was also included in the model. In the logistic regression modeling for the Combined dataset of Efficacy Studies of Gardasil (Studies 007, 013, and 015), the only variable that was nominally statistically significant was Day 1 Pap test result ($p<0.001$). The sponsor postulated that this may indicate that subjects with higher grade Pap abnormalities had higher odds (i.e. risk) of becoming a case of HPV 6/11/16/18 related CIN 2 or worse compared with subjects who had lower grade Pap abnormalities or normal Paps at Day 1. (Source: Efficacy Information Amendment, Regression Analysis, 6/1/06).

When this logistic regression modeling was performed on the Study 013 dataset alone, the variables that were nominally statistically significant were vaccination group ($p=0.041$ for Gardasil group relative to placebo group); region ($p=0.049$ for Asia-Pacific relative to North America, $p=0.001$ for Latin Amerca relative to North America), and Pap test result ($p<0.001$). Thus, there was a nominally higher odds of becoming a case in the Gardasil as compared to the placebo group, and a higher odds of becoming a case in subject from Latin America as compared to subjects from North America.)

Per discussions with CBER statisticians, it is difficult to make any conclusion regarding these data, including the results of the logistic regression analysis. This particular subgroup is a small percentage of the overall population, and is not balanced. Testing for vaccine type specific serology and PCR results are only available in a study setting. Moreover, a truly randomized study in this particular subgroup would be difficult to conduct. It is suspected that the number of subjects that would need to be screened to obtain a reasonable sample size would be large in order to reach adequate power. In addition, the process of screening before randomization is difficult because it is possible that PCR positivity could change between the time of screening and first vaccination (i.e., become PCR positive between the time of screening and first vaccination).

The sponsor has committed to following these subjects over time and evaluate for development of disease in the post-marketing studies. The sponsor has also agreed to conduct additional analyses on the non-naïve subgroups on the close-out of studies 013 and 015.

Effect of Abnormal Pap test at baseline: All Subjects

Data for subjects who developed CIN 2/3 or AIS due to any type HPV was presented as well regarding the effect of an abnormal Pap test and/or naïve or non-naïve HPV status. The sponsor used the MITT-3 and RMITT-3 populations in this comparison. Expanding the RMITT-3 population to include those with a positive or negative Pap test (expanding to MITT-3 population) increased the number of cases of CIN 2/3 by an approximately equal number in both the Gardasil (153) and placebo (157) groups. In addition, the sponsor notes that CIN 2/3 or AIS among women with an abnormal Pap test in the combined studies at baseline accounted for 51% of the cases of CIN 2/3 or AIS detected in the studies. These cases were evenly distributed between the Gardasil and placebo group. Administration of Gardasil to women with pre-existing disease did not appear to have an effect on those with pre-existing Pap test abnormalities. (Source: Amendment 0015, efficacy information amendment submitted 3/22/06 in response to CBER questions sent 3/1/06).]

Effect of including subjects with non-naïve baseline status: All subjects

In the MITT-2 population (naïve subjects) there was one case of HPV 6, 11, 16, and/or 18 related CIN 2/3 or AIS among women who had been administered Gardasil and 69 cases among women who had been administered placebo. When the population was expanded to also include non-naïve subjects (the MITT-3 population) an equal number of cases of HPV 6, 11, 16, and/or 18 related CIN 2/3 or AIS was added to each group. Thus, administration of Gardasil does not appear to increase the number of cases of CIN 2/3 or AIS associated with vaccine HPV type. (Source: Amendment 0015, efficacy information amendment submitted 3/22/06 in response to CBER questions sent 3/1/06; text and Table 1, p. 8).] (See Table 282 below.)

TABLE 282
Protocols 007, 013, 015: Endpoint Counts and Efficacy in the Integrated Phase II/III Efficacy Database for Gardasil

Endpoint	Population	Cases in Vaccine Group	Cases in Placebo Group	Vaccine Efficacy % 95% CI
HPV 6, 11, 16, 18 related CIN 2/3 or AIS	**MITT-2**	**1**	**69**	**99(92,100%)**
	MITT-3	**118**	**186**	**36 (19, 50%)**
CIN 2/3 or AIS	**RMITT-2**	**59**	**96**	**38 (13.56%)**
	RMITT-3	**134**	**171**	**21 (1, 38%)**
	MITT-3	**287**	**328**	**12 (<0, 25%)**

Source: Table 1, Amendment 0015, Efficacy Information Amendment submitted 3/22/06 in response to CBER questions of 3/1/06, p. 8.

Vaccine Efficacy against EGL in Non-Naïve Subjects (Seropositive and/or PCR positive) Subjects

Among non-naïve subjects (seropositive and /or PCR positive for HPV 6, 11, 16, 18) there was no evidence for increased incidence of EGLs. Table 283 presents the efficacy estimates for the subgroups of subjects: seronegative and PCR positive, seropositive and PCR negative; and seropositive and PCR positive. There are fewer cases among those seropositive and PCR negative than among the other subgroups of subjects suggesting that these seropositive subjects may have cleared previous infection(s) and may have

some protection against further EGLs associated with these HPV types. A similar finding was noted for cases of CIN. Overall, there was no evidence for an increased incidence of EGLs in non-naïve subjects in any of the subgroups. Table 283 below presents data from combined exploratory analyses in studies 007, 013, and 015 for the non-naïve subgroups for vaccine HPV type related EGLs.

TABLE 283
Protocols 007, 013, 015 Combined: Analysis of Efficacy Against HPV 6, 11, 16, 18 Related EGLs in Seropositive and/or PCR positive subjects (Subsets of MITT-3 population)

	Gardasil N=9075				Placebo N=9075					
Endpoint Study Population HPV type related EGL	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
Subjects Seronegative &PCR Positive at Day 1										
HPV 6/11/16/18	**810**	**44**	**1530.0**	**2.9**	**782**	**41**	**1482.5**	**2.8**	**-4.0%**	**(-63.2, 33.6%)**
Subjects Seropositive &PCR negative at Day 1										
HPV 6/11/16/18	**1270**	**0**	**2488.8**	**0.0**	**1301**	**4**	**2566.1**	**0.2**	**100.0%**	**(-56.2, 100.0%)**
Subjects seropositive & PCR Positive for relevant HPV type at Day 1										
HPV 6/11/16/18	**336**	**5**	**497.0**	**1.0**	**331**	**5**	**485.3**	**1.0**	**2.4%**	**(-324.3, 77.5%)**

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
Source: Summary of efficacy-external genital lesions, Table 2.7.3:8 8, p. 43 and
Table 7-1, Additional Efficacy Analyses requested by CBER , March 2006, Amendment 0019, 4/7/06

Impact on Pap Test Abnormalities

The evaluation of the impact of vaccination with Gardasil on the incidence of Pap test abnormalities was evaluated in an exploratory analysis as well. Among women with a normal Pap test at baseline (the RMITT-2 population), the point estimate of efficacy in reducing Pap test abnormalities overall is small (10.6%, 95% CI: 3.6, 17.2%). For higher grade lesions, there are some higher point estimates of efficacy in the reduction of ASC-US with a positive probe (20.1%), ASC-H (29.2%), LSIL (13.0%), and HSIL (32.2%), although some without statistical significance.

TABLE 284
Protocols 007, 013, and 015: Impact of Gardasil on Pap Test Abnormalities (RMITT-2 and MITT-3 Populations)

	Gardasil N=9075				Placebo N=9075					
Study Population Pap Abnormality	n	Number of cases	PY at risk	Incidence Rate per 100 person-years at risk	n	Number of Cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
RMITT-2										
ASC-US or worse	5638	1273	10105.2	12.6	5700	1425	10108.0	14.1	10.6%	(3.6, 17.2%)
ASC-US with Positive HPV Probe	5638	207	11171.4	1.9	5700	261	11259.2	2.3	20.1%	(3.7, 33.7%)
ASC-H	5638	54	11279.2	0.5	5700	76	11393.4	0.7	28.2%	(-3.1, 50.3%)
AGC	5638	2	11317.8	0.02	5700	2	11446.6	0.02	-1.1%	(-1295, 92.7%)
LSIL	5638	722	10712.8	6.7	5700	833	10757.2	7.7	13.0%	(3.7, 21.3%)
HSIL	5638	30	11302.5	0.3	5700	45	11415.8	0.4	32.7%	(-9.3, 59.0%)
MITT-3										
ASC-US or worse	8810	2658	14700.3	18.1	8838	2809	14608.8	19.2	6.0%	(0.8, 10.9%)
ASC-US with Positive HPV Probe	8810	544	16077.9	3.2	8838	621	17005.1	3.7	12.3%	(1.4, 21.9%)
ASC-H	8810	133	17343.1	0.8	8838	175	17379.6	1.0	23.8%	(4.0, 39.7%)
AGC	8810	7	17436.3	0.04	8838	8	17500.6	0.05	12.2%	(-1772, 72.9%)
LSIL	8810	1537	15996.6	9.6	8838	1699	15907.9	10.7	10.0%	(3.6, 16.1%)
HSIL	8810	116	17375.4	0.7	8838	125	17425.3	0.7	6.9%	(-20.8, 28.3%)
AIS	8810	2	17440.0	0.01	8838	0	17508.3	0.0	NA	NA

Subjects are counted once in each category, but a subject may appear in more than one category.
N=number of subjects randomized to the respective group who received at least one vaccination.
n=number of subjects in the given population with at least one follow-up visit following 30 days after Day 1.
NA=not assessed
Source: Summary of Efficacy-cervixcancer, Table 2.7.3-cervixcancer: 34, p. 145-6

Impact on Procedures

An exploratory analysis on the impact of vaccination with Gardasil on the frequency of invasive procedures was provided by the sponsor. Among women with a normal Pap at baseline and (and negative for a vaccine HPV type at baseline) (the RMITT-2 population), there appeared to be some reduction in the number of colposcopies in those administered Gardasil compared to placebo (14.9%, 95% CI: 5.3, 23.5%), and there was also evidence of a larger reduction in the number of cervical definitive procedures (28.1%, 95% CI: 2.7, 47.2) and genital lesion definitive therapy (45.7%, 95% CI: 18.3, 64.4%).

When the impact was evaluated in women with normal and abnormal Pap at baseline and regardless of baseline serostatus and/or PCR status, the point estimates for reduction for all procedures were lower as compared to the RMITT-2 population, although there was

evidence of some benefit in the reduction of definitive cervical procedures (16.9%, 95% CI: 2.9, 28.2%) and definitive genital lesion therapy (26.5%, 95% CI: 3.6, 44.2%).

TABLE 285
Protocols 007, 013, and 015: Impact of Gardasil on Selected Invasive Procedures

Population	Cases/Evaluable Subjects		% Reduction (95% CI)
	GARDASIL™	Placebo	
Colposcopy			
RMITT-2	641/5,638	756/5,701	14.9 (5.3, 23.5)
MITT -3	1,726/8,817	1,888/8,848	9.1 (2.9, 14.9)
Colposcopic Biopsy			
RMITT-2	542/5,638	657/5,701	17.2 (7.1, 26.2)
MITT -3	1,461/8,817	1,624/8,848	10.4 (3.8, 16.6)
Definitive Cervical Therapy (e.g., LEEP)			
RMITT-2	76/5,638	107/5,701	28.1 (2.7, 47.2)
MITT -3	322/8,817	387/8,848	16.5 (2.9, 28.2)
Genital Biopsy			
RMITT-2 (FUTURE I)	75/1,726	111/1,733	32.5 (12.8, 52.1)
MITT -3 (FUTURE I)	167/2,671	210/2,668	21.1 (2.8, 36.0)
Genital Lesion Definitive Therapy			
RMITT-2 (FUTURE I)	38/1,726	70/1,733	45.7 (18.3, 64.4)
MITT -3 (FUTURE I)	96/2,671	130/2,668	26.5 (3.6, 44.2)
Note: Point estimates and confidence intervals are adjusted for person time of follow-up. CI = Confidence interval; RMITT = Restricted modified intention to treat; MITT = Modified intention to treat; LEEP = Loop electro-excision procedure; FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease.			

Source: Appendix 2.5:18, p. 74, Clinical Overview

Efficacy Conclusions

There is evidence of efficacy of Gardasil in the prevention of HPV 16, 18, 6, and 11 related cervical dysplastic lesions (CIN 2/3, AIS, or worse). HPV types 16 and 18 have been reported to be associated with approximately 70% of cervical cancers. There is evidence of efficacy against vaccine HPV type related CIN 1 as well.

Highest efficacy rates are noted in subjects who have not been previously exposed to the specific vaccine HPV type prior to administration of Gardasil. In subjects who have been previously infected with a specific vaccine HPV type, there is no evidence of efficacy in reducing cervical dysplasia associated with that vaccine type. However, it appears that efficacy was noted against cervical dysplasia associated with vaccine HPV types to which the subject was naïve.

There is also evidence of efficacy against HPV 6, 11, 16, and 18 related condyloma accuminata, as well as positive effect against HPV 6, 11, 16, and related VIN 2/3 and VaIN 2/3. There is also evidence of benefit against HPV 6, 11, 16, and 18 related VIN 1 and VaIN 1. The progression to vaginal cancer and vulvar cancer from VIN and VaIN lesions is less well defined than the progression of cervical cancer from cervical dysplastic lesions. Not all cases of vulvar cancer are associated with HPV infection, but the association is higher in younger females (the targeted population for this vaccine) as compared to older females.

For vaccine HPV type related external genital lesions, higher efficacy rates are noted in subjects not previously exposed to vaccine HPV types. Because it was possible to exclude a subject with a prior history of an HPV-related external genital lesion (because it was easily diagnosed on external exam), there was a lower proportion of subjects with prevalent disease as compared to those with a history of cervical dysplasia (which could only be diagnosed with a prior Pap test). In addition, a shorter time to development of external genital lesions may also contribute to this observed higher efficacy.

Because of the apparent high efficacy in those naïve to the relevant vaccine HPV types, subjects who are naïve to all 4 vaccine HPV types will likely benefit most from the vaccine. There is no evidence that this group will be protected against disease related to HPV types **not** included in the vaccine, but since HPV 16 and 18 are associated with approximately 70% of cervical cancers, and HPV 6 and 11 with approximately 90% of condylomas, there is expected to be overall benefit in the reduction of CIN 2/3 related to HPV 16 and 18, as well as EGLs related to HPV 6, 11, 16 and 18. Although efficacy studies similar to 005, 007, 013, and 015 were not conducted in young females 9-15 years of age, immunogenicity bridging (which demonstrated non-inferiority of immune response of younger females compared to the response of females 16-26 years of age who participated in the efficacy trials), as well as safety data in the 9-15 year old female population was provided to support use of Gardasil in younger females.

There is no evidence of vaccine efficacy against HPV 16/18 related CIN 2/3 in subjects non-naïve for the relevant vaccine HPV type. An analysis of efficacy in Study 013 in a subgroup of previously infected subjects (seropositive and PCR positive for a specific vaccine HPV type) raised a concern for a negative impact of the vaccine on the incidence rate of cervical disease related to the vaccine HPV type with which they were previously infected. This degree of negative impact was not noted in Study 015. An imbalance in baseline characteristics may have contributed to the higher incidence of HPV 16/18 related CIN 2/3 in Gardasil recipients who were PCR positive and seropositive at baseline as compared to placebo recipients with the same baseline status. (See Executive Summary and discussion earlier in this section.) This negative impact was not noted in the other non-naïve subgroups (seropositive and PCR negative, and seronegative and PCR positive). Further data will be needed to further clarify this issue.

Another concern was that vaccine HPV types would be "replaced" by non-vaccine HPV types. In the study data submitted, there is no clear evidence of replacement disease caused by other non-vaccine HPV types. For example, in the dataset of all subjects who were naïve (seronegative and PCR negative) to any vaccine HPV type and who developed CIN 3 not proven to be associated with a vaccine HPV type at any time after receipt of study material, the numbers of such cases were virtually identical in both treatment groups. The sponsor is in the process of testing biopsy specimens and cervicovaginal swabs for non-vaccine HPV types, and these data are expected to allow for a more definitive conclusion regarding this issue.

The studies also provided some additional epidemiological data on cervical disease (CIN 2/3 or worse) associated with HPV types 16 and 18, and CIN 2/3 or worse associated with HPV types 16 and 18 may represent less than 70% of these cases.

Given the fact that there are more than 100 HPV types, and approximately 30 of these have been reported to be associated with cervical and genital lesions, not all HPV related disease will be prevented, even in persons naïve to all 4 vaccine HPV types. HPV types included in the vaccine have been reported to be associated with most cases of cervical cancer (approximately 70%) and genital warts (approximately 90%). However, because the vaccine does not target all HPV types that have been associated genital disease, females will still require routine gynecological examinations. Further follow-up over time will be needed to evaluate the true impact on HPV related genital disease. Duration of efficacy has not been determined, although detectable antibodies to HPV 16 (anti-HPV 16 antibodies) have been shown to persist at least 4 years in subjects vaccinated in Study 005. (See Immunogenicity Section).

For subjects non-naïve to a specific vaccine HPV type, the sponsor has presented time to event curves which suggest increased benefit to the entire population over time, this may be due to decreased contribution of baseline disease or infection to disease cases. This is suggested by the longer term follow-up data from Study 005 (albeit with monovalent HPV 16 vaccine). The median time of follow-up was less than 2 years in both studies 013 and 015, thus further data will also be required to evaluate the validity of this observation.

Phase III efficacy studies in males and older females are currently ongoing. The post-marketing commitments are listed in the approval letter.

Efficacy against HPV related disease outside the genital tract (i.e, aerodigestive tract disease) has not been studied, although efficacy against these diseases would be of interest to follow in the future.

10 Overview of Safety Across Trials

10.1. Safety Database-Number of Subjects, Types of Subjects, and Extent of Exposure

Monovalent HPV 11, 16, and 18 L1 VLP Vaccines

A total of 3464 subjects were vaccinated in 6 clinical trials. (See Table 286 below)
A total of **2146** subjects were randomized and received at least 1 dose of **Monovalent HPV L1 VLP** vaccines and **1318** were randomized and received at least 1 dose of **placebo.**

TABLE 286
Protocols 001, 002, 004, 005, 006, 012: Overall Extent of Exposure to Monovalent HPV L1 VLP Vaccines

Protocol	Age (years)	Vaccine (Dose Level)	Number of subjects receiving Monovalent HPV vaccine	Number of subjects receiving placebo*
001	18-25	HPV 11 L1 VLP Vaccine (10. 20. 50. 100 mcg/0.5 mL)	112	28
002	18-25	HPV 16 L1 VLP Vaccine (10/40, 40, 80 mcg/0.5mL)	82	27
004	18-25	HPV 16 L1 VLP Vaccine \(20, 40, 80 mcg/0.5 mL)	428	52
005	16-23	HPV 16 L1 VLP Vaccine (40 mcg/0.5 mL)	1193	1198
006	16-23	HPV 18 L1 VLP Vaccine (80 mcg/0.5 mL dose)	27	13
012	16-23	HPV 16 L1 VLP Vaccine (40 mcg/0.5 mL)	304	0
TOTAL	3464		2146	1318

*Placebo = 225 mcg aluminum as amorphous aluminum hydroxide sulfate (AAHS)
Source: Summary of Safety, Table 2.7.4:2, p. 62 (Original BLA)

Quadrivalent HPV 11, 16, and 18 L1 VLP Vaccine

The number of subjects enrolled in Studies 007, 013, 015, 016 and 018 are shown Table 287 below. These are shown by age and gender. 8383 adult females $\geq$ 18 years of age were enrolled in the studies.

TABLE 287
Protocols 007, 013, 015, 016, and 018: Number of Subjects Entered by Age Category and Gender – Safety Populations

Age	Gardasil			Placebo		
	Male N=1077	Female N=10736	Total N=11813	Male N=275	Female N=9426	Total N=9701
≤ 9	67	85	152	38	48	86
10-11	315	354	669	88	89	177
12-13	383	355	738	94	109	203
14-15	311	330	641	55	78	133
16-17	1	1229	1230	0	1156	1156
18-19	0	2493	2493	0	2370	2370
20-21	0	3106	3106	0	3017	3017
22-23	0	2738	2738	0	2522	2522
>23	0	46	46	0	37	37
Mean	12.3	19.2	18.6	11.8	19.8	19.5
SD	1.76	3.14	3.64	1.83	2.52	2.83
Median	12	20.0	19.0	12.0	20.0	20.0
Range	9-16	9-26	9-26	9-15	9-26	9-26

N=Number of subjects randomized in the vaccination group
n=number of subjects within gender/age category
Source: Appendix 2.7.4:6, Summary of Clinical Safety (original BLA) p. 199

3430 subjects 9-17 years of age were enrolled in the study, are shown in Table 288 below.

TABLE 288
Number of subjects 9-17 years of age enrolled by Treatment Group (Males and Females) ***

	Gardasil			Placebo		
Age	Male	Female	Total	Male	Female	Total
9-17 years	1077*	2353	3430	275**	1480	1755
	*Only 1 male ≥ 16 years			**No male > 15 years		

***Does not include 857 female subjects 9-17 years of age who received partial dose formulations in Protocol 016, End-Expiry Substudy. (Source: CSR 016v2 datasets and Efficacy Information amendment 0017 submitted 3/30/06)

The numbers of subjects who received at least one dose of the Gardasil formulation or placebo are shown in Table 289 below. A total of 21,480 subjects were vaccinated in 7 clinical trials. Subjects are counted only once in the integrated summary. A total of 11,792 were randomized and received at least 1 dose Gardasil and 9688 were randomized and received at least 1 dose of placebo. (2 of the placebo recipients received mixed regimens so are not included in Table 289 below). Placebo recipients include those who received alum (vast majority received 225 mcg and 146 subjects in Protocol 007 received 450 mcg doses) and non-alum placebo (N=594).

TABLE 289
Protocols 007, 013, 015, 016, 018:
Overall Extent of Exposure to Gardasil*

Protocol	Age females (years)	Number of female subjects receiving Gardasil	Number of female subjects receiving placebo	Age males (years)	Number of male subjects receiving Gardasil	Number of male subjects receiving placebo
007	16-23	289	292 (a)		0	0
013	16-23	2717	2725(b)		0	0
015	16-26	6082	6075(b)		0	0
016	10-23	1017	0	10-15	508	0
018	9-15	615	320(c)***	9-15	564**	274 (c)***
Total	9-26 years	10720	9412	9-15	1072	274

*Subjects who received at least one dose of full dose study material
**Includes one male ≥ 16 years of age
***1 male and 1 female randomized to receive placebo received mixed regimens in error and are not included in the table.

(a) Placebo: 146 subjects received 225 mcg AAHS (alum) and 146 subjects received 450 mcg AAHS
(b) Placebo = 225 mcg AAHS
(c) Placebo = saline placebo

Source: Summary of Safety, Table 2.7.4:3, p. 65 (Original BLA) and CSR 018v1 Table 11-24, p. 252

Table 290 below shows the number of subjects who received each dose of study material by treatment group, and the reasons for discontinuation. In the safety database totals, males are included to assess adverse events and serious adverse events.

TABLE 290
Protocols 007, 013, 015, 016, 018: Subject Disposition – Safety Population

	Gardasil N/%	Placebo N/%	Total
Screening Failures			1622
Randomized	11813	9701	21514
Vaccinated at:			
Dose 1	11792 (99.8%)	9688 (99.9%)	21480 (99.8%)
Dose 2	11577 (98.0%)	9532 (98.3%)	21109 (98.1%)
Dose 3	11399 (96.5%)	9414 (97.0%)	20813 (96.7%)
Vaccination Period (Day 1 through Month 7)			
Entered	11792	9688	21480
Completed	11328 (96.1%)	9374 (96.8%)	20702 (96.4%)
Continuing	2 (0.0%)	0 (0.0%)	2 (0.0%)
Discontinued	462 (3.9%)	314 (3.2%)	776 (3.6%)
With Long Term Follow-up	56 (0.5%)	31 (0.3%)	87 (0.4%)
AE	6 (0.1%)	7 (0.1%)	13 (0.1%)
Other resaons	31 (0.3%)	9 (0.1%)	40 (0.2%)
Pregnancy	19 (0.2%)	14 (0.1%)	33 (0.2%)
Without Long Term Follow-up	406 (3.4%)	283 (2.9%)	689 (3.2%)
AE	12 (0.1%)	6 (0.1%)	18 (0.1%)
Lost to follow-up	148 (1.3%)	91 (0.9%)	239 (1.1%)
Moved	32 (0.3%)	32 (0.3%)	64 (0.3%)
Other reasons	14 (0.1%)	7 (0.1%)	21 (0.1%)
Parent withdrew consent	14 (0.1%)	8 (0.1%)	22 (0.1%)
Pregnancy	3 (0.0%)	2 (0.0%)	5 (0.0%)
Protocol Deviations	3 (0.0%)	4 (0.0%)	7 (0.0%)
Withdrew consent	180 (1.5%)	133 (1.4%)	313 (1.5%)

Percentages calculated based on the number of subjects who entered the respective period. Includes females and males.
Source: Summary of Clinical Safety (3/8/06), Table 2.7.4:1, p. 141-2, Application Data

Table 291 shows the number and percentage of subjects in each treatment group who entered the safety follow-up period after Month 7. These continue to accrue as time progresses.

TABLE 291
Protocols 007, 013, 015, 016, 018: Subjects in Follow-up Period (after Month 7)

	Gardasil	Placebo	Total
Follow-up period (after Month 7)			
Entered	10382	9387	19769
Completed	697 (6.7%)	257 (2.7%)	954 (4.8%)
Continuing	9556 (92.0%)	9018 (96.1%)	18574 (94.0%)
Discontinued	129 (1.2%)	112 (1.2%)	241 (1.2%)
AE	3 (0.0%)	5 (0.1%)	8 (0.0%)
Lost to follow-up	68 (0.7%)	52 (0.6%)	120 (0.6%)
Moved	13 (0.1%)	14 (0.1%)	27 (0.1%)
Other reasons	4 (0.0%)	4 (0.0%)	8 (0.0%)
Withdrew consent	41 (0.4%)	37 (0.4%)	78 (0.4%)

Source: Summary of Clinical Safety, Table 2.7.4:6, p. 74-75 (original BLA)

Summary of Subject Characteristics: The subject characteristics are provided in Table 292 below. The treatment groups are similar. It is noted that males are not included in the original indication, but they did contribute to the overall safety database for assessment of adverse events and SAEs. Males are therefore included in the totals shown in Table 292 below.

TABLE 292
Protocol 007, 013, 015, 016, and 018: Summary of Subject Characteristics by Vaccination Group –Safety Population (Application Data)

	Gardasil N=11813*	Placebo N=9701*	Total N=21514*
Gender	N/%	N/%	N/%
Female	10736 (90.0%)	9426 (97.2%)	20162 (93.7%)
Male	1077 (9.1%)	275 (2.8%)	1352 (6.3%)
Age (years)			
Median	19	20	20
Range	9-26	9-26	9-26
Weight (kg)			
Median	58	59	59
Range	19-161	22-146	19-161
BMI			
Median	22	22	22
Range	9-79	13-51	9-79
Race/Ethnicity			
Asian	662 (5.6%)	381 (3.9%)	1043 (4.8%)
Black	468 (4.0%)	434 (4.5%)	902 (4.2%)
Hispanic American	1589 (13.5%)	1274 (13.1%)	2863 (13.3%)
Native American	18 (0.2%)	13 (0.1%)	31 (0.1%)
White	8144 (68.9%)	6706 (69.1%)	14850 (69.0%)
Other	932 (7.9%)	893 (9.2%)	1825 (8.5%)
Region			
Asia-Pacific	847 (7.2%)	421 (4.3%)	1268 (5.9%)
Europe	5202 (44.0%)	4726 (48.7%)	9928 (46.1%)
Latin America	3329 (28.2%)	2902 (29.9%)	6231 (29.0%)
North America	2435 (20.6%)	1652 (17.0%)	4087 (19.0%)
Smoking Status			
Current Smoker	2542 (21.5%)	2465 (25.4%)	5007 (23.3%)
Ex-smoker	693 (5.9%)	736 (7.6%)	1429 (6.6%)
Never Smoked	6373 (53.9%)	5899 (60.8%)	12272 (57.0%)

Source: Summary of Clinical Efficacy, Appendix 2.7.4:2, p. 144-145 (3/8/06)
*N's represent the number of subjects who were randomized.

In the females 16-26 years of age who were included in the safety population (Gardasil N=9612, Placebo N=9102), 26.9% were seropositive and/or PCR positive to one of the vaccine HPV types. The breakdown of subjects is shown in Table 293 below.

TABLE 293
Protocols 007, 013, 015, and 016: Summary of Composite HPV 6, 11, 16, and 18 Status by PCR and/or Serology at Day 1 by Vaccination Group — Female Subjects 16 to 26 Years of Age at Enrollment in the Safety Population

Day 1 Composite HPV 6/11/16/18 Status	Gardasil N=9612	Placebo N=9102	Total N=18,714
	m/n (%)	m/n (%)	m/n (%)
Negative to HPV 6, 11, 16, and 18 By serology and PCR	6493/9480 (73.2%)	6570/8997 (73.0%)	13513/18477 (73.1%)
Positive to HPV 6, 11, 16, and 18 By serology and PCR	2537/9480 (26.8%)	2427/8997 (27.0%)	4964/18477 (26.9%)

*Percentage calculated based on number of subjects with satisfactory Pap test
**Percentages of SIL calculated based on number of subjects with a satisfactory Pap test at Day 1
N=number of subjects randomized
Source: Table 2.7.4:8, Summary of Clinical Safety, original BLA, p. 78

Safety Populations

Detailed Safety Population: This population is a subset of the General Safety Population (see below). The Detailed Safety Population included subjects in Protocols 007, 013 (including 011 and 012), the NSAE substudy participants of Protocol 015, and subjects in Protocols 016 and 018 who completed a Vaccine Report Card to report Adverse Events in the 14 days after each vaccination.

General Safety Population: This population was followed for SAEs, although they did also report adverse events that occurred at the time of the following visit. The General Safety population had a lower percentage of subjects with any adverse event as compared to subjects in the Detailed Safety Population. The number (percentage) of subjects with an SAE in the General Safety Population (which includes the Detailed Safety Population) was slightly higher in the Gardasil group. The number (percentage) of subjects in the Detailed Safety Population with an SAE was slightly lower in the Gardasil group as compared to the placebo group. (See Tables 295 and 296 below)

TABLE 294
Protocols 007, 013, 015, 016, 018: Subjects included in Clinical Adverse Event Summary (Days 1-15 after any Vaccination)

Population	Gardasil	Placebo
General Safety Population	11778*	9686
Detailed Safety Population	6160	4064

Source: Summary of Clinical Safety, Table 2.7.4:11 and 12, p. 84-87 (11/05)
*This N represents the number of subjects in the entire Safety Population who received Gardasil, excuding subjects who received vaccination regimens in violation of the protocol

TABLE 295
Protocols 007, 013, 015, 016, and 018: Clinical Adverse Experience Summary (Days 1 to 15 after any Vaccination Visit) - Safety Population (Cumulative Data)

	Gardasil N=11778	Placebo N=9686
Subjects with Follow-up	11641	9578
	N/%	N/%
Subjects with ≥ 1 AE	5729 (49.2%)	3659 (38.2%)
Injection Site AEs	5195 (44.6%)	3049 (31.8%)
Systemic AEs	3750 (32.2%)	2571 (26.8%)
Subjects with SAEs	59 (0.5%)	43 (0.4%)
Deaths	3 (0.03%)	1 (0.01%)
Discontinued due to AE	15 (0.1%)	10 (0.1%)
Discontinued due to SAE	4 (0.03%)	3 (0.03%)

Source: Source: Summary of Clinical Safety, Table 2.7.4:4, p. 29 (3/8/06)

TABLE 296
Protocols 007, 013, 015, 016, and 018: Clinical Adverse Experience Summary (Days 1 to 15 after any Vaccination Visit) - Detailed Safety Population (Cumulative Data)

	Gardasil N=6160	Placebo N=4064
Subjects with Follow-up	6069	3994
	N/%	N/%
Subjects with ≥ 1 AE	5455 (89.9%)	3416 (85.5%)
Injection Site AEs	5035 (83.0%)	2932 (73.4%)
Systemic AEs	3591 (59.2%)	2413 (60.4%)
Subjects with SAEs	37 (0.6%)	26 (0.7%)
Deaths	1 (0.02%)	1 (0.03%)
Discontinued due to AE	11 (0.2%)	6 (0.2%)
Discontinued due to SAE	2 (0.0%)	2 (0.1%)

Source: Summary of Clinical Safety, Table 2.7.4:5, p. 30 (3/8/06)

The data included Tables 295 and 296 above refers to **Days 1-15 days** after any vaccination, and thus the lower number of deaths and discontinuations as compared to the details provided in the subsequent sections regarding deaths and discontinuations due to an AE, which reported on all such events throughout the study period.

10.2 Safety Assessment

Vaccine Report Cards: Safety was evaluated using Vaccination Report Card (VRC) surveillance for 14 days after each injection of HPV vaccine or placebo in Protocols 007, 013 (including 011 and 012), 016 and 018). In addition, in Protocol 015, only a subset of subjects was followed using VRC surveillance (Detailed Safety Population) and the remainder of the subjects used general surveillance methodology. The General Safety population includes subjects with VRC surveillance and general surveillance.

Temperature: Temperature values were recorded for 5 days (Day 1 through Day 5 postvaccination). Any temperature value ≥100°F or ≥37.8°C, oral equivalent, was

considered an adverse experience of fever. Feeling "feverish" was also recorded as having a fever.

Injection Site Adverse Events: Injection-site adverse experiences of pain/tenderness, swelling, and redness were prompted for on the VRC for 5 days (Day 1 through Day 5 postvaccination). Other injection-site adverse experiences occurring from Day 1 through Day 5 and injection-site adverse experiences occurring from Day 6 through Day 15 were also recorded, but not prompted.

Systemic Adverse Events: Systemic adverse experiences were recorded for 15 days (Day 1 through Day 15 postvaccination). In Protocol 018 only, systemic adverse experiences of sore or aching muscles, sore or aching joints, headaches, hives or other rash, and diarrhea were also prompted on the VRC for 15 days (Day 1 through Day 15 postvaccination).

Causality: The investigator determined relationship to vaccine administration.

Grading: The grading was assessed by the subject (mild, moderate, severe). Any redness or swelling was measured (with ruler on VRC). Mild was 0 - $\leq$ 1 inch; moderate was > 1 to $\leq$ 2 inches; and severe was > 2 inches.

Serious Adverse Events (SAEs):
Serious adverse experiences were required to be reported to the sponsor within 24 hours of the investigator becoming aware of the event for all subjects. The following were reported as SAEs:

- Any SAE for day of consent to 14 days postdose 1, and 14 days postdose 2 and 3 regardless of attribution
- Any death or SAE which resulted in study discontinuation, or AE that was life-threatening
- Any SAE throughout study which was possibly vaccine or procedure related or whose relationship was unclear
- Pregnancy related SAEs were reported throughout study, as well as congenital anomalies
- Cancers and overdoses were also reported.

Pregnancy and Lactation
For all studies, pregnancies were followed for outcomes. In addition, for Phase III studies, administration of study vaccine/placebo to lactating women followed for outcomes. Serious adverse experiences in infants born to study subjects were reported to the clinical database.

New Medical Conditions were reported during the vaccination period (Day 1 through Month 7) and after the vaccination period (post-Month 7).

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

There were 10 deaths in the Gardasil recipients (0.8%), and 7 deaths in the placebo group (0.7%). The majority of the deaths were due to trauma in both groups. These deaths did not appear related to vaccine administration.

In each treatment group, there was a death related to a deep vein thrombosis and/or pulmonary embolism, and both subjects were on hormonal contraceptives. The Gardasil recipient with this event had symptoms of leg pain prior to the first vaccination. The other Gardasil recipients who died included one subject with pancreatic cancer 578 days after dose 3, and one young male who died of arrhythmia 27 days after dose 1. This latter subject had a strong family history for arrhythmia. These events did not appear related to administration of the vaccine.

TABLE 297
Protocols 007, 013, 015, 016, 018: Deaths

	Gardasil N=11778	Days postdose	Placebo N=9680	Days postdose
Trauma	4 19 y/o f 23 y/o f 20 y/o f 22 y/o f	 373 days postdose 3 8 days postdose 2 90 days postdose 3 800 days postdose 3	3 18 y/o f 17 y/o/f 16 y/o f	 2 day postdose 2 342 days postdose 3 798 days postdose 3
DVT/PE	1 (22 y/o f)	19 days postdose 1	1 (23 y/o f)	202 days postdose 2
Sepsis, DIC	1 (21 y/o f)	359 days postdose 3		
Pneumonia, sepsis	1 (21 y/o f)	625 days postdose 3		
Pancreatic cancer	1 (25 y/o f)	578 days postdose 3		
Arrythmia	1 (15 y/o m)	27 days postdose 1		
Convulsion, drug use	1 (21 y/o f)	4 days postdose 3		
Suicide			2 17 y/o f 21 y/o f	 200 days postdose 3 517 days postdose 3
Asphyxiation post C-section (took meds, was in tub)			1 (18 y/o f)	256 days postdose 2
Total Percentage of subjects	10 (0.08%)		7 (0.07%)	

Source: Summary of Clinical Efficacy, Table 2.7.4:20, p. 56-61 (3/8/06)

10.3.2 Serious Adverse Events

In the General Safety population, 102 subjects who received Gardasil and 99 subjects who received Placebo developed an SAE during the course of the study. Table 298 below shows the SAE events by organ system. In review of the SAEs reported in the Safety Update, there were 136 events in the Gardasil group and 125 events in the placebo group. One subject may have had more than one SAE. Some events were noted twice in the same subject, or a number of events in one subject were related to one major event, so these were combined into one event during review. Thus, the totals shown in Table 298 are 116 events in the Gardasil group and 115 events in the placebo group.

Exclusion of subjects with inadvertent administration of excess study material: When the 34 subjects with SAEs due to inadvertent administration of excess study material are excluded, there are 87/11778 subjects in the Gardasil group with an SAE (0.7%) and 80/9680 subjects in the placebo group with an SAE (0.8%).

The obstetrical/gynecology category included the largest number of SAEs in each treatment group. The types of SAEs appear generally comparable. There are somewhat more GI events in the Gardasil group as compared to the placebo group. There are 4 episodes of appendicitis which occurred at variable times post-vaccination in the Gardasil group.

Asthma/bronchospasm occurred in 3 Gardasil recipients and 0 placebo recipients. These events occurred 1 day postdose 1, 9 days postdose 2, and 1 day postdose 3. All recovered. One SAE of interest was cutaneous vasculitis, which occurred 10 days after the third dose of Gardasil and the subject recovered. One subject in the placebo group suffered an anaphylactic reaction 12 days postdose 1.

TABLE 298
Protocols 007, 013, 015, 016, 018: SAEs by Organ Systems
(All Subjects, Cumulative Data, 3/8/06)

Organ System Event	Gardasil N=11778	Days postdose	Organ System Event	Placebo N=9680	Days postdose
GYN					
Cervix dystocia	5 [42260]	426 days postdose 2 254 days postdose 1 255 days postdose 2 251 days postdose 3 356 days postdose 2	Cervix dystocia	1	345 days postdose 2
Transverse presentation	1	403 days postdose 2			
Premature labor	4 [24658] [49458]	215 days postdose 1 231 days postdose 3 277 days postdose 3 161 days postdose 1	Premature labor	5[56634]	248 days postdose 3 282 days postdose 2 312 days postdose 2 225 & 243 days postdose 1 240 & 262 days postdose 1
Pre-eclampsia	2 [24658] [56349]	251 days postdose 1 260 days postdose 3	Pre-eclampsia	4	283 days postdose 1 279 days postdose 2 242 days postdose 2 301 days postdose 3
Prolonged Labor	2 [24815] [33168]	272 days postdose 3 348 days postdose 2			
CPD	2 [33168]	264 days postdose 1 348 days postdose 2	CPD	6[40119] [49473]	277 days postdose 1 347 days postdose 2 283 days postdose 3 378 days postdose 2 266 days postdose 3 304 days postdose 1
PROM	3 [42260]	550 days postdose 3 255 days postdose 1 356 days postdose 2	PROM	1	271 days postdose 2
Fetal distress syndrome	2 [41060] [49458]	284 days postdose 3 247 days postdose 1 257 days postdose 1	Fetal distress syndrome Neonatal asphyxia	3 1[45433]	254 days postdose 2 247 days postdose 3 255 days postdose 3 297 days postdose 3
Breech presentation	1	261 days postdose 2	Breech Presentation	2[56634]	325 days postdose 2 298 days postdose 2

TABLE 298 [Cont.] Protocols 007, 013, 015, 016, 018: SAEs by Organ Systems (All Subjects, Cumulative Data, 3/8/06)

Organ System Event	Gardasil N=11778	Days postdose	Organ System Event	Placebo N=9680	Days postdose
GYN (CONT.)					
Post-procedural hemorrhage	1	1 day postdose 2	Post-procedure hemorrhage	2 [24058]	911 days postdose 3 575 days postdose 3
Dysfunctional uterine bleeding with anemia	1	11 days postdose 2	Cervix hemorrhage uterine	2 [24058]	918 days postdose 3 422 days postdose 3
Failed trial labor	3 [42410]	268 days postdose 3 286 days postdose 1 261 days postdose 3	Failed induction/trial labor	5[40119] [49473]	341 days postdose 2 302 days postdose 3 347 days postdose 2 262 days postdose 1 304 days postdose 1
PID	2 [31101]	6 days postdose 2 1 day postdose 2	PID	2	5 days postdose 1 25 days postdose 1
Condyloma acuminata	1	15 days postdose 2			
Fetal malposition	1	272 days postdose 1 (with operative hem.)	Fetal malpresentation	2[56428] [45433]	252 days postdose 2 297 days postdose 3
Oligohydramnios	2 [56349]	617 days postdose 1 261 days postdose 3	Oligohydramnios	1	265 days postdose 1
Threatened abortion	3	25 days postdose 2 45 days postdose 1 63 days postdose 1	Threatened abortion	6[32282]	105 days postdose 1 121 days postdose 1 53 days postdose 2 158 daus postdose 2 217 days postdose 2 70 days postdose 1
Endometritis	1	116 days postdose 1	Endometritis	1	271 days postdose 3
			Umbilical cord around neck	1 [32282]	305 days postdose 1
Pregnancy Induced hypertension	2	316 days postdose 2 243 days postdose 2	Pregnancy induced hypertension	1 [56019]	303 days postdose 3
Failed forceps delivery	1	413 days postdose 2			
Contractions during pregnancy	1[43659]	266 days postdose 2			
Hyperemesis gravidarum	2 [41060]	42 days postdose 3 37 & 53 days postdose 1			
Ovarian cyst	2	12 days postdose 2 14 days postdose 2			
Postpartum hemorrhage	1	315 days postdose 3			
Cervicitis	1	230days postdose 2			
Ectopic pregnancy	1	61 days postdose 3	Ectopic pregnancy	1	39 days postdose 3
			Uterine infection	1	94 days postdose 1
			Cervical incompetence	1	191 days postdose 3
			Prolonged Pregnancy	2	325 days postdose 2 292 days postdose 1
			Vaginal laceration	1	7 days postdose 3
Vaginal hemorrhage	1 [62075]	26 days postdose 1 & 42 days postdose 3			
Gyn Events	(49)		Gyn Events	(51)	

TABLE 298 [Cont.] Protocols 007, 013, 015, 016, 018: SAEs by Organ Systems (All Subjects, Cumulative Data, 3/8/06)

Organ System Event	Gardasil N=11778	Days postdose	Organ System Event	Placebo N=9680	Days postdose
GI					
Pancreatic CA	1 (7494)*	578 days postdose 3			
Appendicitis	4 [42410]	1 day postdose 2 42 days postdose 2 183 days postdose 3 (pregnant) 2 days postdose 2	Appendicitis	1	14 days postdose 2
Cholecystitis/cholelithiasis	2	5 days postdose 1 3 days postdose 2			
Gastroenteritis	3	8 days postdose 1 13 days postdose 3 5 days postdose 2	Gastroenteritis, GI infection	2	1 day postdose 2 3 day postdose 1
Reflux espohagitis	1	2 dayspostdose 1			
Abdominal pain	1[43659]	94 days postdose 2	Abdominal pain	1	111 days postdose 2
Abdominal pain, diarrhea and vomiting	1	9 days postdose 1			
			Gastritis	1	43 days postdose 2
Total GI	(13)		Total GI	(5)	
GU					
Renal colic	1	9 days postdose 3			
Pyelonephritis	2 [24815]	7 days postdose 3 43 days postdose 3	Pyelonephritis	1	30 days postdose 2
			Renal failure	1 [24657*]	204 days postdose 3
UTI	2 [31101]	6 days postdose 2 229 days postdose 2	Kidney infection or UTI	3[56019]	8 days postdose 1 7 days postdose 3 323 days postdose 3
			Urinary Retention	1	44 days postdose 1
Renal failure acute (post-op)	1	6 days postdose 1			
Total GU Events	(6)		Total GU Events	(6)	
Heme					
Anemia	1 [24658]	251 days postdose 1			
Total Heme Events	(1)				
Infection					
			Varicella	1	175 days postdose 1
Sepsis, infective thrombosis, DIC	1 (44256)*	359 days postdose 3			
			Typhoid fever	1	30 days postdose 2
			Pyrexia, chills, Headache	1	1 day postdose 2
Foot infection	1	2 days postdose 2			
Tonsillitis (Streptococcal)	1	7 days postdose 1			
Total Infection Events	(3)		Total Infection Events	(3)	

TABLE 298 [Cont.] Protocols 007, 013, 015, 016, 018: SAEs by Organ Systems (All Subjects, Cumulative Data, 3/8/06)

Organ System Event	Gardasil N=11778	Days postdose	Organ System Event	Placebo N=9680	Days postdose
Neuro					
			Facial palsy	1	373 days postdose 3
Convulsion with drug use	1 (47711)*	4 days postdose 3	Convulsion	1[20325]	3 days postdose 2
Headache	3 [56349]	11 days postdose 2 1 day postdose 3 2 days postdose 3	Headache	1 [20325]	3 days postdose 2
Dizziness	1	5 days postdose 2	Dizziness	1	44 days postdose 2
			Syncope	1	1 day postdose 1
Total Neuro Events	(5)		Total Neuro Events	(5)	
Pulmonary					
			ARDS	1 (24657*)	204 days postdose 3
Asthma	2	1 day postdose 1 9 days postdose 2	(Anaphylaxis see immune mediated)	(1)	
Bronchospasm	1	1 day postdose 3			
Hyperventilation	1	15 days postdose 1			
Pneumonia/sepsis	1 (54003)*	625 days postdose 3			
			Asphyxia	1 (56248)*	256 days postdose 2
			Pneumomediastinum	1	275 days postdose 1
Pneumonia	1	5 days postdose 1	Pneumonia	1	14 days postdose 1
Total Pulm Events	(6)		Total Pulm Events	(4)	
Psych					
Depression	1	2 days postdose 3			
Bipolar disorder	1	105 days postdose 3			
Overdose	1	13 days postdose 2	Suicide, 1 with overdose	2	517 days postdose 3 200 days postdose 3
Total Psych Events	(3)		Total Psych events	(2)	
CV					
Thrombophlebitis	1	4 days postdose 2			
Hypotension	1	295 days postdose 1			
Hypertnesion	1 [56349]	1 day postdose 3			
			Aortic valve disease with hypertension	1	2 days postdose 3
DVT/PE	1 (44507)*	19 days postdose 1	DVT/PE	1 (24657*)	202 days postdose 3
Arrythmia	1 (64196)*	27 days postdose 1			
Total CV Events	(5)		Total CV Events	(2)	
Immune mediated					
Cutaneous vasculitis	1	10 days postdose 3			
			Hypersensitivity	1	1 day postdose 2
			Anaphylactic reaction	1	12 days postdose 1
			Face edema	1	4 days postdose 3
Total Immune	(1)		Total Immune	(3)	

TABLE 298 [Cont.] Protocols 007, 013, 015, 016, 018: SAEs by Organ Systems (All Subjects, Cumulative Data, 3/8/06)

Organ System Event	Gardasil N=11778	Days postdose	Organ System Event	Placebo N=9680	Days postdose
ENDO					
			Thyroid cancer	1	7 days postdose 2
Diabetes mellitus	1	2 days postdose 1			
Total Endo Events	(1)		Total Endo Events	(1)	
Musculoskeletal					
Injection site movement impairment	1	1 day postdose 2	Extremity pain	1	13 days postdose 3
Total musculoskeletal **(within day ranges for SAE reports)**	(1)		Total musculoskeletal	(1)	
Trauma/Injury					
Head injury	1 (25212)*	373 days postdose 3			
			Poisoning (Accidental)	2	427 days postdose 3 15 days postdose 3
MVA	1(40327)* 1(46973)* 1(55537)*	800 days postdose 3 8 days postdose 2 90 days postdose 3	MVA	3 (25378*) (43687*) (46856*)	 2 days postdose 2 798 days postdose 3 342 days postdose 3
			Abdominal injury	1	14 days postdose 3
Polytrauma	1(30663)*	10 days postdose 1			
			Intervertebral disc protrusion	1	10 days postdose 1
Total Trauma events	(5)		Total Trauma Events	(7)	
Skin					
			Contact Dermatitis	1	12 days postdose 1
Total Skin Events	(0)		Total Skin Events	(1)	
Excess study vaccine	17 [30938:2] [30940:2]	Day of dosing 1,2, 3	Excess study vaccine [30937:2, 30941:2, 30942:2, 30943:2, 30944:2]	24	Day of dosing 1,2, 3
Total excess study vaccine events	(17)		Total excess study events	(24)	

[ ] indicate ANs of subjects with more than one SAE
Source: Summary of Clinical Efficacy, Table 2.7.4:20, p. 63-102 (3/8/06)
Note: Numbers were updated for both Gardasil and placebo groups in the 3/8/06 submission.
( )*Deaths

10.3.3 Discontinuations due to an Adverse Event

Discontinuations due to an AE were also comparable between the groups. There were 42 subjects overall who discontinued due to an AE. These included 24 subjects in the Gardasil group (0.20%) and 18 in the placebo group (0.19%). These totals included 9 subjects in the Gardasil group and 7 subjects in the placebo group who discontinued due to death (included in Table 298 above). The Gardasil recipients who discontinued due to an AE (excluding deaths) are shown in Table 299 and the placebo recipients who discontinued due to an AE are shown in Table 300.

TABLE 299
Protocols 007, 013, 015, 016, and 018: Subjects who Received Gardasil and Discontinued from their Studies (Excluding Deaths)*

Event	Days postdose	Outcome
Swelling face (severe) Swelling face (moderate)	6 days postdose 1 10 days postdose 1	Recovered
Diarrhea Nausea Vomiting	9 days postdose 1 9 days postdose 1 9 days postdose 1	Pt. with history of GE reflux (on aciphex prior to vaccination); reported nausea, vomiting and diarrhea with menses. It is noted that subject d/c'd from study and declined to return for early disconuation visit
Urticaria (severe)	1 day postdose 1	Recovered
Injection site swelling (Grade 2)	1 day postdose 2	Recovered
Dizziness (moderate) Dizziness (severe) Injection site erythema (2)	2 days postdose 2 2 days postdose 2 2 days postdose 2	Recovered
Bronchial irritation	1 day postdose 1	Recovered
Polyarthritis ***DX: Carpal tunnel syndrome**	21 days postdose 1	Not recovered **For surgery**
Rash (moderate)	2 days postdose 1	Recovered
RA (severe)	**40 days postdose 2**	**Not recovered ****
Rash (moderate)	1 day postdose 1	Recovered
Injection site pain (mild) Vomiting (moderate)	1 day postdose 1 5 days postdose 1	Recovered
Diarrhea (moderate) Lymphadenopathy (mild)	4 days postdose 1 8 days postdose 1	Recovered
Acute renal failure (moderate)	6 days postdose 1	Recovered
Injection site pain (moderate)	1 day posdose 1	Recovered
Injection site swelling (4)	1 day postdose 2	Recovered

*Excludes deaths

Source: From Table 2.7.4:19, p. 113-20, clinical summary safety and Summary of Clinical Efficacy, Table 2.7.4: 23, p. 106-116 (3/8/06)

TABLE 300
Protocols 007, 013, 015, 016, and 018: Subjects Who Received Placebo and Discontinued From their Studies*

Event	Days postdose	Outcome
Hypoaesthesia (mild)	2 days postdose 2	Recovered
Injection site pain (mild)	33 days postdose 2	Recovered
Herpes zoster (severe)	43 days postdose 2	Recovered
Allergic edema (severe)	3 days postdose 1	Recovered
Eczema (moderate)	3 days postdose 2	Recovered
Syncope (severe)	20 seconds postdose 1	Recovered
Injection site reaction (mild)	30 minutes postdose 1	Recovered
Pyrexia (moderate)	6 days postdose 1	Recovered
Influenza (mild)	1 day postdose 1	Recovered
Hypersenstivity (moderate)	1 day postdose 2	Recovered
Pyrexia and eczema (moderate)	2 and 5 days postdose 2	Recovered

(Source: From Table 2.7.4:19, p. 113-20, clinical summary safety and Summary of Clinical Efficacy, Table 2.7.4: 23, p. 106-116 (3/8/06)

In the Safety Update Report (SUR) follow-up period (after the SUR cut-off dates for EXT 007 and further follow-up of studies 011, 012, and 015), there was one subject with an SAE in the blinded group for 007 EXT (Tylenol OD for leg pain after injection, resolved; had leg pain after previous doses of Gardasil in the primary series which lasted 1 day each) and one subject in the placebo group with an SAE (30361, 012, vaginal beeding post 2 LEEPS).

10.3.4 Autoimmune Disorders

An AE of interest was the case of rheumatoid arthritis which occurred 40 days after the second dose of Gardasil in an 18 year old female participating in Study 016 (see case discussed below). In addition, there was a case of cutaneous vasculitis (which resolved). When reviewing the new medical conditions in the 7 month vaccination period, it is noted that there were slightly more cases of arthropathy in the Gardasil group as compared to the placebo group. (The terms used were from MedDRA.) The Unified Medical Language System defines arthropathies as "condition in which there is a deviation from or interruption of the normal structure or function of the joints". The groups were similar for this outcome in the post-Month 7 period. An analysis by the sponsor estimated the incidence of arthritis and related conditions to be similar to the background rate in the general population. Reports on cases were requested from the sponsor, and these were submitted to the BLA.

JRA

There were three subjects who reported a history of JRA prior to vaccination (and these were included in Prior medical history). All 3 were in the Gardasil group. Their disease did not reactivate after vaccination.

One subject developed juvenile arthritis after enrollment. This was noted during the review of new medical conditions included in the BLA. AN 71311, a 14 year old white female from the UK was enrolled in Protocol 018. She had complained of back pain at Day 1 prior to vaccination. She received Gardasil x 2 doses. She complained of mild

injection site pain and irritable colon after the second dose (time not specified further). At Month 6, she was found to have a low grade inflammatory arthropathy. At Month 6, her labs showed an ESR of 4 mm/hr (normal) and C-reactive protein of 5 mg/L (normal) and an elevated RF of 93 IU/mL (normal < 20). The subject began treatment with methylprednisolone. This was the 1 incident case of JRA in the trial. According to the sponsor, the annual incidence rates are noted to vary from 0.8 – 22.6/100,000. In the UK, the annual incidence of JRA is estimated to be 10/100,000 children under the age of 16 years of age. In the US, the incidence is reported to be 50-100/100,000.[13] The sponsor calculated the incidence in the trials to be 55/100,000 (although there was only 1 incident case).

Rheumatoid Arthritis

Across all Gardasil trials, 8 RA cases were reported. 5 (2 Gardasil and 3 placebo) of the 8 were present at Day 1 and were considered pre-exisiting conditions. One other subject had symptoms evident at Day 1. AN 45652, a 20-year old white female from Sweden reported RA at Month 6, but at Day 1, reported active pain in her arms, fingers, and knees. It was, therefore, considered to be present prior to vaccination.
The other two cases were considered to be incident cases of RA.
One subject (AN 45279), a 16 year old female in Finland participating in Protocol 015, received 3 doses of Gardasil and at Month 24 was diagnosed with RA. Medications included predisone.

Another subject, AN 61116, an 18 year old female randomized to receive Gardasil in Protocol 016, developed left wrist pain approximately 40 days after the second dose of vaccine (doses administered 6/13/03 and 8/15/03). (This subject was reported in the group that discontinued due to AE, but was not reported as an SAE because the investigator judged the RA was not of sufficient severity to meet the criteria for an SAE.) This resolved after 3-4 days, then was followed by pain in the left shoulder. Over the next months, the pain became persistent, in her wrists, shoulders, knees, ankles, toes, and left hip. There was a family history of fibromyalgia in her mother, and hypothyroidism in her sister. In November 2003, her RF and ANA were normal, her ESR was 8 mm/hr and an ASLO titer was negative. She was evaluated by a rheumatologist 12/18/03. She was started on Naprosyn. Labs in 12/03 showed an ESR of 35 mm/hr, C-reactive protein of 1.8 mg/dL, and a mildly positive RF of 22. When seen again in January 2004, she had improved somewhat on the Naprosyn, but still had joint discomfort. Prednisone and methotrexate were added to her regimen. She improved. A follow-up visit was reported for 2/13/06. She had no joint pains, but continued on 7.5 mg po methotrexate weekly, and there were no residual signs of arthritis or symptoms of joint pains or stiffness. Methotrexate was tapered further to 5 mg po weekly. The investigator assessed that the AE was possibly due to study vaccine.

The sponsor calculated with the 2 incident cases reported above, the incidence was 10.4 cases /100,000. The annual incidence rate for RA in women 15-25 years of age is calculated to be app. 10-15 cases/100,000. The annual overall incidence is 70 per

[13]From Medline Plus, http://www.nlm.nih.gov/medlineplus/ency/article/000451.htm

100,000 subjects, and the prevalence in the US population is 1-2%.[14] The incidence in the study was therefore what would be expected in a young female population.
Most of the subjects who developed RA (although not all) had pre-vaccination complaints of joint pain. Post-marketing commttments will focus on similar adverse events in a larger population.

Others
Scleroderma: One subject (AN 24077, Protocol 011-020, Fydek-Mistek), an 18 year old white female who received placebo was diagnosed with scleroderma at Month 2, but this subject had rash and sun sensitivity at Day 1. This was therefore thought to be a pre-existing condition.

SLE:
There was one subject (AN 45027), a 22 year old Asian female participating in Protocol 015, who had active arthritis on Day 1 and was being treated with chondriotin sulfate sodium + glucosamine hydrochloride+ ibuprofen at that time. She received 3 doses of Gardasil and reported a diagnosis of SLE at Month 24. She subsequently received diclofenac and rofecoxib. It was, therefore, thought that the disease was already present at day 1 given the subject's arthritis which predated vaccination.

A case of SLE did develop in a subject (17 year old white female in Finland) who received placebo (AN 43810, Protocol 015). She was diagnosed with SLE at Month 24. Lab testing and medications are not available for this subject.

The sponsor estimated the incidence of SLE as 2.5 per 100,000 subjects (with a background incidence of 1.0-7.6/100,000 estimated in the US).

Non-specific Inflamatory Conditions
Arthritis
Across all clinical trials of Gardasil, 11 cases of arthritis were reported. Of these, 4 were present at Day 1 (3 Gardasil and 1 placebo).
Among the remaining 7, 5 were reported in Gardasil recipients and 2 were reported in placebo recipients.
AN 9258, 22 year old white female in Finland in protocol 007, received Gardasil. She reported arthritis at Month 24, but had also complained of back pain at day 1. No further data were available.
AN 44822, a 17 year old white female in Finland in Protocol 015, received Gardasil, and reported arthritis at the Month 6 visit. This subject had acute symptoms which resolved.
AN 62639, a 10 year old white female in Brazil in Protocol 016 received Gardasil and reported arthritis and Left wrist pain at the Month 6 visit. No cause was listed, but she was treated with physiotherapy alone.
AN 47865, a 19 year old Hispanic female in Colombia in protocol 015 who received Gardasil and reported arthritis at Month 24. The cause was listed as autoimmune but no further data were available.

[14] From Johns Hopkins Arthritis Center website, http://www.hopkins-arthritis.som.jhmi.edu/rheumatoid/rheum_clin_pres.html

AN 31626, an 18 year olf white female in the US in Protocol 012 received Gardasil and reported arthritis at Month 24. This was classified as palindromic (relapses and remits). This subject had complained of arthralgia at day 1 in her wrists and ankles (which had ben attributed to a snowboarding accident). It is possible that this arthritis was secondary to trauma suffered prior to enrollment.
Therefore in the Gardasil group, 1 case of arthritis was considered autoimmune at Month 24. In the 4 other cases, one resolved spontaneously, one was possibly related to trauma, one was localized and required physiotherapy alone, and one subject may have had symptoms at Day 1.
In the placebo group, one subject had left toe arthritis reportedly not due to an injury at Month 12, and one subject had chondromalacia patellae diagnosed at Month 18.

Reactive arthritis
There was one subject in the placebo group with a preexisting case of reactive arthritis at Day 1.
A Gardasil recipient, AN 44987, is a 21 year old white female in Sweden was diagnosed with reactive arthritis at Month 7 due to an unspecified infection.

Polyarthritis
Two subjects were diagnosed with polyarthritis. One subject had these symptoms at Day 1 (received Gardasil). One subject had polyarthitis at 21 days postdose 1 Gardasil, but was subsequently diagnosed as having **carpal tunnel syndrome** which was treated with surgery.

The overall rates of incident conditions potentially indicative of systemic autoimmune disorder after enrollment in Gardasil clinical trials are presented in Table 301 below.

TABLE 301
Protocols 005, 007, 013, 015, 016, 018: Summary of Subjects Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder after Enrollment in clinical trials of Gardasil
(At Any Time During Trial)

Potential autoimmune disorder	Gardasil N=11813	Placebo N=9701
Specific terms	3 (0.025%)	1 (0.010%)
Juvenile arthritis	1	0
Rheumatoid arthritis	2	0
SLE	0	1
Other terms	6 (0.051%)	2 (0.021%)
Arthritis	5	2
Reactive arthritis	1	0
Polyarthritis	0	0

Source: Amendment 0017, Efficacy Information Amendment, 3/30/06

The incidence of events diagnosed after vaccination that may be related to autoimmune processes appears to be similar to incidence of these events reported in the general population. In addition, 3 of the subjects listed with "Other terms" who received Gardasil may have had joint pains related to trauma, and 1 may have had symptoms related to arthritis present at Day 1. In addition, the 1 case of incident JRA in the Gardasil group may also have had symptoms (back pain) at Day 1. Nonetheless, because of this potential safety concern, CBER has requested that immune related conditions be monitored for 6 months after vaccination in the large manage care organization short term follow-up post marketing commitment study.

CBER also requested additional information on cases of autoimmune thyroiditis. The sponsor provided responses in Amendment 0017 to the BLA (3/30/06). Across all studies, 10 casess of autoimmune thyroiditis were reported. 5 of these were reported at Day 1 (2 in the Gardasil group and 3 in the placebo group). (Of the remaining 5 cases that were reported in New medical conditions, 4 were reported in the Gardasil group and 1 in the placebo group.) However, 1 in the Gardasil group (AN 42337, a 21 year old female participating in Protocol 015) had reported active thyroiditis at Day 1. Therefore, there were 3 cases in the Gardasil group and 1 in the placebo group. **(The amendment for this analysis was submitted 3/30/06, in Amendment 0017, after the original BLA and after the safety update information).**
AN 70545 (Protocol 018): A 12 year old Asian male from Thailand reported Hashimoto's thyroiditis at Month 2. Labs included antithyroglobulin antibody and antithyroid peroxidase antibody increase with otherwise normal TFTs. The subject received all 3 vaccinations and is continuing in the study.
AN 71809 (Protocol 018): A 12 year old white male in the US reported autoimmune thyroiditis at Month 12 (received all 3 doses of vaccine). He was noted to be hypothyroid with an elevated antithyroid peroxidase antibody level. The subject received L-thyroxine with decrease in TSH. This subject had a family history of hypothyroidism (mother). The subject completed the study.

AN 47198 (Protocol 015): 22 year old white female in Poland received all 3 doses of Gardasil and reported Hashimoto's thyroiditis at Month 24. She is currently continuing in the study.
AN 30037 (Protocol 012/013): A 21 year old white female in the US received 3 doses of placebo and reported Hashimoto's thyroiditis at Month 36. She is currently continuing in the study.

The incidence rate of autoimmune thyroiditis observed in the study population was comparable with incidence rates reported in the literature (the observed incidence rate in the Gardasil recipients was 14.3/100,000 subjects compared to the annual incidence rate reported in the literature of 30-150 cases per 100,000). Nonetheless, this will be assessed in the large post-marketing managed care study.

10.3.5 New Medical History (Day 1 through Month 7) (Source: Appendix 2.7.4:60, p. 569-660, not shown here) [Medical terms are from MedDRA version 7.1.]

- The most commonly reported new medical conditions were nasopharyngitis, headache, and vaginal candidiasis.
- The proportions of subjects who developed new medical conditions were generally comparable between the 2 groups.
- Table 302 below presents the most common new medical conditions and those of interest (with slight inequality between vaccine and placebo)
- No obvious safety signal was identified from these data.

TABLE 302
Protocols 007, 013, 015, 016 and 018:
New Medical Conditions Day 1 through Month 7 in the Safety Population

Subjects in analysis population	Gardasil N=11778	Placebo N=9686
Subjects with new medical history	5842 (49.6%)	4750 (49%)
Blood and Lymphatic	99 (0.8%)	88 (0.9%)
Anemia	68 (0.6%)	68 (0.7%)
Cardiac	11 (0.1%)	12 (0.1%)
Endocrine	20 (0.2%)	17 (0.2%)
Autoimmune thyroditis	1 (0.0%)	0 (0.0%)
Basedow's disease	2 (0.0%)	0 (0.0%)
Eye	118 (1.0%)	72 (0.7%)
Conjunctivitis	61 (0.5%)	36 (0.4%)
Uveitis	1 (0.0%)	0 (0.0%)
GI	710 (6.0%)	638 (6.6%)
Abdominal Pain	91 (0.8%)	74 (0.8%)
Diarrhea	121 (1.0%)	88 (0.9%)
Gastritis	100 (0.8%)	110 (1.1%)
Nausea	76 (0.6%)	79 (0.8%)
Crohn's	0 (0.0%)	1 (0.0%)
Ulcerative Colitis	0 (0.0%)	2 (0.0%)
Immune	150 (1.3%)	112 (1.2%)
Drug Hypersensitivity	20 (0.2%)	18 (0.2%)
Hypersensitivity	26 (0.2%)	24 (0.2%)
Infection	3469 (29.5%)	2963 (30.6%)
Influenza	345 (2.9%)	298 (3.1%)
Nasophrayngitis	598 (5.1%)	513 (5.3%)
Pharyngitis	162 (1.4%)	135 (1.4%)
Tonsillitis	158 (1.3%)	138 (1.4%)
URI	226 (1.9%)	123 (1.3%)
UTI	254 (2.2%)	298 (3.1%)
Vaginal Candidiasis	389 (3.3%)	369 (3.8%)
Vaginal infection	132 (1.1%)	166 (1.7%)
Vaginitis bacterial	356 (3.0%)	323 (3.3%)
Musculoskeletal and CTD	387 (3.3%)	256 (2.6%)
Arthralgia	61 (0.5%)	35 (0.4%)
Arthritis	2 (0.0%)	0 (0.0%)
Arthritis Reactive	1 (0.0%)	0 (0.0%)
Arthropathy	6 (0.1%)	1(0.0%)
RA	1 (0.0%)	0 (0.0%)
Neoplasm	68 (0.6%)	50 (0.5%)
Hodgkin's disease	1 (0.0%)	0 (0.0%)
Neurological	681 (5.8%)	495 (5.1%)
Headache	527 (4.5%)	374 (3.9%)
Psych	167 (1.4%)	162 (1.7%)

TABLE 302 [Cont.] Protocols 007, 013, 015, 016 and 018: New Medical Conditions Day 1 through Month 7 in the Safety Population

Subjects in analysis population	Gardasil N=11778	Placebo N=9686
Depression	56 (0.5%)	51 (0.5%)
Renal	121 (1.0%)	121 (1.2%)
Reproductive and Breast Disorders	1284 (10.9%)	1224 (12.6%)
Amenorrhea	113 (1.0%)	99 (1.0%)
Dysmenorhhea	136 (1.2%)	96 (1.0%)
Ectropion of cervix	140 (1.2%)	110 (1.1%)
Menstruation irregular	157 (1.3%)	159 (1.6%)
Metrorrhagia	138 (1.2%)	151 (1.6%)
Vaginal discharge	244 (2.1%)	231 (2.4%)
Respiratory	379 (3.2%)	234 (2.4%)
Cough	104 (0.9%)	70 (0.7%)
Pharynolaryngeal pain	119 (1.0%)	64 (0.7%)
Skin	382 (3.2%)	302 (3.1%)
Surgical and medical Procedures	384 (3.3%)	296 (3.1%)
Appendectomy	19 (0.2%)	4 (0.04%)

(Source: From Appendix 2.7.4:60, p. 569-660, Summary Clinical Safety [11/05]),

The majority of neoplasms were benign in both treatment groups.
There was a higher proportion of appendectomies in the Gardasil group in the initial 7 month follow-up period, but there was a higher proportion in the post-Month 7 period in the placebo group.

New Medical History (post Month 7)

- The most commonly reported new medical conditions after the vaccination period were vaginal infections and discharge.
- The percentages of subjects in each group who developed new medical conditions after the vaccination period were generally comparable.
- Table 303 below presents the most common new medical conditions and those of interest (with slight inequality between vaccine and placebo)

TABLE 303
Protocols 007, 013, 015, 016 and 018:
New Medical Conditions after Month 7 in the Safety Population

Subjects in analysis population	Gardasil N=10452	Placebo N=9385
Subjects with new medical history	5178 (49.5%)	4883 (52.0%)
Blood/Lymph	145 (1.4%)	136 (1.4%)
Anemia	108 (1.0%)	104 (1.1%)
Cardiac	20 (0.2%)	13 (0.1%)
Endocrine	33 (0.3%)	33 (0.4%)
Autoimmune thyroiditis	3 [2]* (0.0%)	1 (0.0%)
Basedow's disease	2 (0.0%)	1 (0.0%)
Goiter	4 (0.0%)	2 (0.0%)
Hypothyroidism	15 (0.1%)	16 (0.2%)
Eye	82 (0.8%)	78 (0.8%)
Conjunctivitis	45 (0.4%)	54 (0.6%)
Uveitis	1 (0.0%)	0 (0.0%)
GI	634 (6.1%)	595 (6.3%)
Abdominal pain	136 (1.3%)	120 (1.3%)
Crohn's disease	4 (0.0%)	0 (0.0%)
Ulcerative colitis	2 (0.0%)	0 (0.0%)
Diarrhea	70 (0.7%)	71 (0.8%)
Gastritis	113 (1.1%)	111 (1.2%)
Nausea	49 (0.5%)	47 (0.5%)
Immune system	87 (0.8%)	88 (0.9%)
Infections	3349 (32%)	3265 (34.8%)
Cervicitis	164 (1.6%)	170 (1.8%)
Cystitis	230 (2.2%)	229 (2.4%)
Gastroenteritis	106 (1.0%)	122 (1.3%)
Gyn Chlamydia infection	201 (1.9%)	238 (2.5%)
Influenza	203 (1.9%)	205 (2.2%)
Nasopharyngitis	260 (2.5%)	259 (2.8%)
PID	154 (1.5%)	151 (1.6%)
Pharyngitis	139 (1.3%)	116 (1.2%)
Sinusitis	143 (1.4%)	133 (1.4%)
Tonsilitis	94 (0.9%)	91 (1.0%)
URI	167 (1.6%)	168 (1.8%)
UTI	429 (4.1%)	416 (4.4%)
Vaginal candidiasis	589 (6.6%)	645 (6.9%)
Vaginal infection	181 (1.7%)	193 (2.1%)
Vaginitis bacterial	522 (5.0%)	512 (5.5%)
Vulvitis	87 (0.8%)	93 (1.0%)
Musculoskeletal and CTD	240 (2.3%)	242 (2.6%)
Arthralgia	29 (0.3%)	29 (0.3%)
Arthritis	3(0.0%)	2 (0.0%)
Arthropathy	1 (0.0%)	0 (0.0%)
Back Pain	87 (0.8%)	90 (1.0%)

TABLE 303 [Cont.] Protocols 007, 013, 015, 016 and 018:
New Medical Conditions after Month 7 in the Safety Population

Subjects in analysis population	Gardasil N=10452	Placebo N=9385
Juvenile arthritis	1 (0.0%)	0 (0.0%)
Neoplasm	78 (0.7%)	67 (0.7%)
GU neoplasm (reported as benign)	1 (0.0%)	0 (0.0%)
Hodgkin's disease	1 (0.0%)	0 (0.0%)
Neuro	269 (2.6%)	217 (2.3%)
Headache	114 (1.1%)	86 (0.9%)
MS	1 (0.0%)	2 (0.0%)
Psych	199 (1.9%)	203 (2.2%)
Depression	87 (0.8%)	82 (0.9%)
Renal	144 (1.4%)	135 (1.4%)
Dysuria	72 (0.7%)	71 (0.8%)
Reproductive	1574 (15.1%)	1590 (16.9%)
Amenorrhea	131 (1.3%)	128 (1.4%)
Ectropion of cervix	97 (0.9%)	125 (1.3%)
Menstruation irregular	165 (1.6%)	199 (2.1%)
Vaginal discharge	363 (3.5%)	351 (3.7%)
Respiratory	172 (1.6%)	154 (1.6%)
Asthma	29 (0.3%)	29 (0.3%)
Cough	42 (0.4%)	41 (0.4%)
Skin	312 (3.0%)	303 (3.2%)
Surgery	477 (4.6%)	495 (5.3%)
Appendectomy	17 (0.2%)	26 (0.3%)
Vascular disorders	45 (0.4%)	38 (0.4%)
Hypertension	21 (0.2%)	8 (0.1%)

Source: From Appendix 2.7.4: 61, p. 661-761, Clinical summary of safety

*[One Gardasil recipient with autoimmune thyroiditis at Month 12 had thyroiditis prior to vaccination, so the number should be [2] instead of 3. – Source: Amendment 0017, submitted 3/30/06 to BLA].

It was noted that there were 4 cases of Crohn's post Month 7 in the Gardasil group and 0 in the placebo group. It is noted that in New Medical conditions Day 1 to Month 7, there were 0 cases of UC in the Gardasil group and 2 in the placebo group, and 0 cases of Crohn's in the Gardasil group and 1 in the placebo group.

In the 2 subjects with Hodgkin's disease, one subject had a family history of a lymphoproliferative disorder.

An overall comparison of new medical conditions is noted in Table 304 below.

TABLE 304
Protocols 007, 013, 015, 016, 018: New Medical Conditions (Number and Percent) During Vaccination Period through Month 7 and after Month 7 for Selected Organ Systems

Organ System	During Vaccination Period		Post Month 7	
	Gardasil N=11778	Placebo N=9868	Gardasil N=10452	Placebo N=9385
Blood and Lymphatic	99 (0.8%)	88 (0.9%)	189 (1.8%)	136 (1.4%)
Cardiac	11 (0.1%)	12 (0.1%)	20 (0.2%)	13 (0.1%)
Endocrine	20 (0.2%)	17 (0.2%)	33 (0.3%)	33 (0.4%)
Eye	118 (1.0%)	72 (0.7%)	82 (0.8%)	78 (0.8%)
GI	710 (6.0%)	638 (6.6%)	634 (6.1%)	595 (6.3%)
Immune	150 (1.3%)	112 (1.2%)	87 (0.8%)	88 (0.9%)
Infection	3472 (29.5%)	2963 (30.6%)	3800 (36.3%)	3265 (34.8%)
Musculoskeletal	387 (3.3%)	256 (2.6%)	240 (2.3%)	242 (2.6%)
Neoplasms	68 (0.6%)	50 (0.5%)	78 (0.7%)	67 (0.7%)
Nervous System	681 (5.8%)	495 (5.1%)	269 (2.6%)	217 (2.3%)
Psychiatric	167 (1.4%)	162 (1.7%)	199 (1.9%)	203 (2.2%)
Renal	121 (1.0%)	121 (1.2%)	159 (1.5%)	135 (1.4%)
Reproductive	1287 (10.9%)	1224 (12.6%)	1722 (16.5%)	1590 (16.9%)
Respiratory	380 (3.2%)	234 (2.4%)	223 (2.1%)	154 (1.6%)
Surgical	382 (3.2%)	296 (3.1%)	477 (4.6%)	495 (5.3%)
Appendectomy	19 (0.2%)	4 (<0.l%)	17 (0.2%)	26 (0.3%)
Vascular disorders	27 (0.2%)	39 (0.4%)	45 (0.4%)	38 (0.4%)

Source: Summary of Clinical Safety (BLA): Appendices 2.7.4:60 and 61

Reviewer's Comment: The N's for the "During Vaccination" period and the "Post Month 7" Period are different because not all subjects who participated in studies in the vaccination period continued on to the post month 7 period, and not all who continued past Month 7 provided additional safety data. Most of the subjects in each treatment group did not continue because of loss to follow-up, withdrawal of consent, or movement out of the study site area. Very few in each group discontinued due to an AE.

10.3.6 Pregnancy

Subjects were tested for pregnancy prior to each vaccination, and if found to be pregnant, vaccination was postponed. However, a fair number of subjects in each group did become pregnant during the study.

Adverse Events in Pregnancy (Gardasil)

- A similar pattern and occurrence of SAEs and AEs in pregnancy were reported in women who were vaccinated with Gardasil (N=40, 4.2%) or placebo (N=41, 4.3%). The most common events reported were conditions that led to C-section (failure labor, malpresentation, CPD), premature onset labor (threatened abortions, PROM), and pregnancy related problems (pre-eclampsia, hyperemesis). The SAEs were uncommon, and the rates were similar between the Gardasil and placebo groups. (**In the SAE table, events were presented rather than subjects.)**
- The AE profile for women who became pregnant during the clinical studies is shown in Table 305 below. The number of subjects who became pregnant and were analyzed

for safety through pregnancy is small. The proportions of subjects more closely resemble those of the General Safety Population.

- There was a higher proportion of AEs, injection site AEs, and systemic AEs in Gardasil recipients who became pregnant during the vaccination period as compared to those who received placebo.
- The proportion of Gardasil recipients with elevated Ts was higher as compared to placebo recipients.

TABLE 305
Adverse Events in Those who Became Pregnant During the Vaccination Period (Compared to Detailed Safety Population and Safety Population), Days 1-15 Following Any Vaccination Visit

	Safety Population (007, 011, 012, 013, 015, 016, 018) (a)		Detailed Safety Population (007, 011, 012, 013, 015, 016, 018) (b)		Subjects who were pregnant during the vaccination period (011, 012, 013, 015, 016) (c)	
	G N=11778	P N=9686	G N=6160	P N=4064	G N=230	P N=235
Subjects with f/u	11640	9578	6069	3994	223	229
1+ AE	5729 49.2%	3659 38.2%	5455 89.9%	3416 85.5%	112 50.2%	86 37.6%
Systemic	3750 32.2%	2571 26.8%	3591 59.2%	2413 60.4%	67 30.0%	58 25.3%
Subjects with SAEs	59 0.5%	43 0.4%	37 0.6%	26 0.7%	3 1.3%	3 1.3%

Source: (a) Table 2.7.4:4, p. 29, Summary of Clinical Safety update 3/8/06;
(b) Table 2.7.4:5, p. 30, Summary of Clinical Safety update 3/8/06;
(c) Table 2.7.4:30, p. 130, Summary of Clinical Safety, original BLA

The proportion of subjects with spontaneous abortions are similar between the two treatment group. (See Table 306 below).

TABLE 306
Protocols 013, 015, 016, 018: Pregnancy Outcomes in the Phase III studies

	Gardasil N=10418	Placebo N=9120
Subjects with pregnancies	1115 (10.7%)	1151 (12.6%)
Number of pregnancies	1244	1272
Number of fetuses/infants with known outcomes	996	1018
Number of pregnancies with unknown outcomes	258	263
Live Births	621 (62.3%)	611 (60.0%)
Infant Outcome		
Normal	570 (91.8%)	569 (93.1%)
Abnormal	49 (7.9%)	40 (6.5%)
Congenital Anomaly	14 (2.3%)	12 (2.0%)
Other Medical Conditions	39 (6.3%)	28 (4.6%)
Unknown	2 (0.3%)	2 (0.3%)
Fetal Loss	375 (37.7%)	407 (40.0%)
Type of Loss		
Spontaneous miscarriage	249 (25%)* (66.4% of fetal loss)	257 (25.2%)* (63.1% of fetal loss)
Late Fetal Deaths	11 (2.9% of fetal loss)	8 (2.0% of fetal loss)
Elective abortions	114 (30.4%)	142 (34.9%)
Fetal Outcome		
Normal	18 (4.8%)	11 (2.7%)
Abnormal	8 (2.1%)	14 (3.4%)
Congenital anomaly	0 (0.0%)	2 (0.5%)
Other Medical Conditions	7 (1.9%)	10 (2.5%)
Unknown	348 (92.8%)	382 (93.9%)

*Percentage calculated with number of known outcomes
Source: Summary of Clinical Safety (3/8/06): Table 2.7.4:24, p. 126-8

Congenital Anomalies

Congenital anomalies which occurred in the clinical trials are included in Table 307 below.

TABLE 307
Protocols 005, 007, 013, 015, 016*: Gardasil Recipients vs. Placebo Recipients Whose Infants had Congenital Anomalies (Through 11/05)

Gardasil			Placebo		
AN	EDCn Relative to Vaccination	Congenital Anomaly	AN	EDCn Relative to Vaccination	Congenital Anomaly
24658	1/postdose 1	Hip dysplasia	31309	54/postdose 3	Congenital hip deformity, exomphalos, ASD
33319	2/predose 2	Congenital hydronephrosis	33947	95/postdose 3	VSD, ASD
41894	7/postdose 3	Congenital megacolon	49420	104/postdose 3	Hip dysplasia
45992	9/postdose 1	Talipes	24458	118/postdose 3	Exomphalos
30580	19/postdose 1	Congenital Ankyloglossia, pyloric stenosis	46118	166/postdose 3	VSD
47851	33/postdose 1	Heart disease congenital, duodenal atresia, trisomy 21 **(F)**	24772	214/postdose 3	Bilateral inguinal hernia
56355	57/postdose 2	Anomalous pulmonary venous connection **(F)**	32072	292/postdose 3	Congenital hydronephrosis
47862	116/postdose 2	Persistent fetal circulation	40330	343/postdose 3	Amniotic band syndrome **(F)**
40450	212/postdose 3	Branchial cyst	31132	377/postdose 3	Adactyly
24836	285/postdose 3	Low set ears, limb malformation **(F)**	30287	378/postdose 3	Cleft lip and palate
25428	332/postdose 3	Tricuspid valve incompetence	47257	379/postdose 3	Polydactyly
55443	351/postdose 3	Cardiac murmur	46561	498/postdose 3	Congenital anomaly **(F)**
43445	477/postdose 3	Partial trisomy 16 and partial monosomy 9, kidney malformation, kidney duplex, ASD, VSD	32464	464/postdose 3	Mandibulofacial dysostosis (Diagnosed subsequently as Treacher Collin syndrome)
31701	792/postdose 1	Ear malformation	46120	843/postdose 3	G6PD deficiency
43702	601/postdose 3	Atrioventricular valve defect	47866	442/postdose 2	Exomphalos
Protocol 004**	App. 1 month postdose 1 Monovalent 16	Tracheomalacia	25201	426/postdose 3	Congenital hernia

*There were no reported pregnancies in Protocol 018 Day 0 through Month 7. There was 1 elective termination with the Month 12 safety update.

**From Protocol 004 with 10 mcg dose of HPV 16 L1 VLP vaccine. This case is not included in the next table.

F=fatal

Overall, in the Safety Update as of 3/8/06, the number of congenital anomalies were balanced between the Gardasil and placebo groups. There was 1 case of tracheomalacia in a child whose mother received 10 mcg HPV 16 app. 1 month prior to conception (Protocol 004). If this anomaly is added to the total, there would be 16 in each group from the original BLA).
(NOTE: The child with the cardiac murmur also had dyspnea at Day 1, and was diagnosed with a congenital anomaly. They were awaiting a cardiology consult.)

There were additional infants with congenital anomalies that were reported after the Safety Update Report cutoff dates (EXT 007 - 11/30/05 and for 011, 012, and 015 - 11/11/05) through January 25, 2006.

- In the Gardasil group, there was 1 child born to subject AN 32615, study 012, with renal agenesis (reported in good health). The child was born 28 months after the last dose of Gardasil.
- There were 3 additional congenital anomalies and 1 neoplasia in infants born to mothers who received placebo in the additional safety follow-up period. These included:
  - AN 8284 (007 EXT): Renal cyst 34 months postdose 3 placebo.
  - AN 54823 (015): Patent ductus arteriosus with pulmonary hypertension 27 months postdose 3 placebo.
  - AN 57053 (015): Right auricular agenesis 27 months postdose 3 placebo.
  - AN 24923 (011): Right atrial neoplasia 17 months postdose 3 placebo and Hepatitis B vaccine (fatal).

These congenital anomalies and events occurred well after apparent estimated dates of conception. The total number of anomalies would be amended to **17 for the Gardasil group and 19 for the placebo group (plus one additional neoplasia)**.

TABLE 308

Distribution of Congenital Anomaly Cases in the Phase III Clinical Database by EDCn Timing in Relation to Study Vaccination and by Time When the Diagnosis Was Made, by Vaccination Group
(Protocols 011, 012, 013, 015, 016, and 018)
(CUM Data)

	GARDASIL™	Placebo
Infant/Fetuses Congenital Anomalies	**15**	**16**
EDCn within 30 days of a study vaccination	**5**	**0**
Live birth reported in the neonatal period	5	0
Live birth reported beyond the neonatal period	0	0
Fetal loss	0	0
Intra-uterine diagnosis	0	0
EDCn beyond 30 days of a study vaccination	**10**	**16**
Live birth reported in the neonatal period	8	12
Live birth reported beyond the neonatal period	1	1
Fetal loss	0	2
Intra-uterine diagnosis	1	1

EDCn = Estimated Date of Conception.

Source: Summary of Safety, Table 2.7.4:26, p. 135 (3/8/06)

One issue of concern is the occurrence of 5 of the anomalies in children whose mothers received vaccine within 30 days of estimated date of conception. There were 5 such subjects in the Gardasil group and 0 in the placebo group with exposure within 30 days of the estinated date of conception. Upon review, it was noted the anomalies that occurred in this proximate time period were in different organ systems. The congenital anomalies were reviewed by a geneticist from the ---------- arranged by Merck. His blinded and unblinded assessments were included in the BLA package, and the anomalies that occurred within 30 days of the estimated date of conception were assessed as probably not or definitely related to study material. The sponsor reported that hip dysplasia, talipes, and pyloric stenosis were unlikely to have been related because these events usually occur later in pregnancy than at the times of exposure indicated. Congenital hydronephrosis due to a problem with the uretero-pelvic junction would be expected to occur at 5 weeks gestation, and if this anomaly occurred at the time of exposure noted, more diffuse anomalies might have been expected to have occurred. Congenital megacolon is associated with neural crest development, which does occur within the first 30 days of gestation, but again, more extensive anomalies would have been expected to occur if due to vaccine exposure at 7 days postdose 3. There was one infant with an EDCn of 33 days prior to vaccination. This infant had Trisomy 21 (Down's syndrome), for which there is no known teratogenic cause, and the other anomalies reported (heart disease and duodenal atresia) are known to occur with Down's syndrome.

Medical Conditions Other Than Congenital Anomalies Reported in Live Born Infants and Fetal Losses of Subjects enrolled in Phase III Program

Serious Adverse Events Reported in Infants of Vaccinated Subjects who were potentially exposed to test product (Entire Study Period) Safety Population

The sponsor reported the SAEs which occurred during the neonatal period (typically defined as the first 27 days of life) and SAEs that occurred other than the neonatal period or the lactation period. **The SAEs in the neonatal period (see congenital anomalies table for infants with congenital anomalies) are shown in Table 309 below.** On review of the table provided (3/8/06 safety update), there were 37 subjects with 38 infants with SAEs noted in the Gardasil group and 34 subjects with 34 infants with an SAE in the placebo group in this period. As of 3/8/06 and with SUR follow-up report, there were 621 + 3 (624) live births in the Gardasil group and 611 + 4 (615) in the placebo group. In review of the SAEs in infants in the neonatal period, there were 43 subjects with 44 (44/624 = 7.1%) infants in the Gardasil group with 62 SAEs (one infant had 8 SAEs). For the placebo group, there were 38 subjects with 38 (38/615 = 6.2%) infants and 47 SAEs. There are more infants with Neonatal Respiratory Distress Syndrome (NRDS) in the placebo group as compared to the Gardasil group, 5 vs. 2 respectively, and are not apparently temporally related to receipt of vaccine by mother. (Note: One of the two infants with NRDS in the Gardasil group occurred in a child with a congenital anomaly and does not appear in Table 309 below).

TABLE 309
Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (Cumulative Data)**
[Excludes Congenital Anomalies]

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Neonatal jaundice					
	24016 (011)	722 d postdose 3/1 d (R)	With convulsion, elctrolyte imbalance	[24801] (011)	748 d/postdose 3/ 5d (R)
	41651 (012)	327 d postdose 2/7d (R)	With mandibulofacial dysotosis	[32464] (012)	267 d postdose 1/ 1 d (C)
	47833 (015)	339 d postdose 2/4 d (R)		31756 (012)	262 d postdose 2/ 1 d (R)
	49146 (015)	679 d postdose 3/7 d (R)	With dyspnea and sepsis	[33039] (012)	274 d postdose 1/ 1d (R)
	57020 (015)	258 d postdose 1/2d (R)		46684 (015)	434 d postdose 3/ 9d (R)
With NRDS	[31702] (012)	743 d postdose 3/1d (R)		46686 (015) hyperbilirubinemia	380 d postdose 3/2d (R)
With prematurity	[25142]** (011)	521 d postdose 3/1d (R)	Neonatal jaundice	45889 (015)	18 months postdose 3 placebo/5 days old (R)
With GE reflux	[32138]* (012)	29 months postdose 3 Gardasil/few days old (R)	Neonatal jaundice	45895 (015)	27 months postdose 3 placebo (R)
	43173** (015)	23 months postdose 3/few days old (R)			
	30804	30 months postdose 3, 4 days of age (R)			
Neonatal jaundice	30804 (012)	30 months postdose Gardasil/4 days of age (R)			

TABLE 309 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (Cumulative Data) [Excludes Congenital Anomalies]**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Neonatal sepsis					
With neonatal anoxia	[24815] (011)	278 d postdose 3/1 d (R)	With dyspnea and neonatal jaundice	[33039] (012)	274d postdose 1/1d (R)
With prematurity, fetal growth retardation, bronchiolitis	[54184] (015)	270-298 d postdose 3/1d-28 d **(F)**	With neonatal apnea and prematurity	[45950] (015)	778 d postdose 3/1 d (R)
			With prenatarity, meningitis	[47745] (015)	262-268 d postdose 1/1d-7d (R)
Prematurity					
With jaundice, transient tachypnea, atelectasis	[25142] (011)	515d postdose 3/1d (R)		25312 (011)	643 d postdose 3/1d **(F)**
	48154 (015)	231d postdose 3/1 d (R)		34207 (011)	249 d postdose 2/1 d (R)
	55036 (015)	608 d postdose 3/1 d (R)	With NRDS	[30588] (012)	346 d postdose 3/1d (R)
	48412 (015)	693 d postdose 3/1d (R)		57596 (015)	232 d postdose 2/1d (R)
	40184 (015)	719 d postdose 3/1d (C)		41439 (015)	731 d postdose 3/1d (R)
	56439 (015)	261 d postdose 3/ 1d (R)		45487 (015)	710 d postdose 3/1 d (R)
With fetal growth retardation, neonatal sepsis, bronchiolitis	[54184] (015)	270-298 d postdose 3/1-28d **(F)**	With apnea, sepsis	[45950] (015)	778 d postdose 3/1 d (R)
With SVT	[45005] (015)	771 d postdose 3/ 1d (R)		56634 (015)	312 d postdose 2/1 d (R)
	48741 (015)	309 d postdose 3/ 1d (R)		43015 (015)	756 d postdose 3 /1d (R)
	48230 (015)	224 d postdose 2 /d1 (R)	With congenital toxoplasmosis	[48234] (015)	428 d postdose 3/1d (R)

TABLE 309 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (Cumulative Data) [Excludes Congenital Anomalies]**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	AN (study)	Event	Time after dose/age (Outcome)
Prematurity (Cont.)					
				47415 (015)	243 d postdose 1/1d (R)
			With sepsis, meningitis	[47745] (015)	262-268 d postdose 1/1-7d (R)
Small for dates					
	20497 (011)	658 d postdose 3/1d (R)		20386 (011)	698 d postdose 3/1d (R)
	49427 (015)	563 days postdose 3/1d (R)			
	43303 (015)	376 d postdose 3/1d (R)			
NRDS					
With neonatal jaundice	[31702] (012)	743 d postdose 3/1d (R)		24399 (011)	248 d postdose 3/1d (R)
			With prematurity	[30588] (012)	346 d postdose 3/1d (R)
				31762 (012)	757 d postdose 3/1d (R)
				33432 (012)	622 days postdose 3/1d (C)
				40161 (015)	262 d postdose 1/1d (R)
Transient tachypnea, dyspnea, asthma of newborn					
Transient tachypnea with prematurity, jaundice	[25142] (011)	515-521 d postdose 3/1d (R)	Asthma	20516** (011)	416 d postdose 3/31 d (R)
Transient tachypnea	25271 (011)	245 d postdose 1/1d (R)	Dyspnea (with jaundice, sepsis)	[33039] (012)	274 d postdose 1/1 d (R)
Dyspnea	45780 (015)	370 d postdose 2/1 d (R)			

TABLE 309 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to test product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (Cumulative Data) [Excludes Congenital Anomalies]**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	AN (study)	Event	Time after dose/age (Outcome)
Respiratory events/infection					
Neonatal aspiration	31291	305 d postdose 1/1d (R)	Respiratory tract infection	24995 (011)	671 d postdose 3/19 d (R)
Neonatal aspiration	49548 (015)	247 d postdose 1/1d (R)	Neonatal pneumonia	41516 (015)	800 d postdose 3/1d (R)
Neonatal pneuomonia	45236** (015)	679 d postdose 3/2 d (R)	Neonatal aspiration	42196 (015)	305 d postdose 3/1d (R)
Neonatal pneumonia	47969 (015)	702 d postdose 3/3d (R)	Fetal distress syndrome	49299 (015)	722 d postdose 3/1d (R)
Neonatal asphyxia (with dehydration, hypoglycemia)	[40391] (015)	286 days postdose 1/1 d (R)	Pneumonia, Low birth weight	30479 (012)	21 months postdose 3 placebo (R)
Bronchiolitis	32536 (012)	386 d postdose 2/47 d (R)			
Others					
Rh incompatability	31030 (012)	934 d postdose 3/1d (R)	Convulsion with jaundice, electrolyte imbalance	[24801] (011)	748 d postdose 3/5 d (R)
Neonatal infection (mild)	32296 (012)	246 d postdose 1/1d (R)	UTI	25224 (011)	293 d postdose 3/32d (R)
Neonatal hypocalcemia	31954 (012)	867 d postdose 3/1d (R)	Pyrexia	33122 (012)	680 d postdose 3/1d (R)
Necrotozing enterocolitis with varicella	33405 (012)	374 d postdose 3/1d (R)	Neonatal hypoglycemia	46453 (015)	327 d postdose 2/d 3 (R)
Twins: female with E. coli infection; male with E. coli infection, GE reflux, vesicourteral reflux, sleep apnea	57822** (015)	715 d postdose 2/18 d (E. coli R, others (C)	SVT	43363 (015)	732 d postdose 3/29 d (C)
Neonatal infective mastitis	40397 (015)	767 d postdose 3/21 d (R)	GE Reflux	56019 (015)	305 d postdose 3/1d (R)

TABLE 309 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to Test Product – Entire Study Period* (Systemic-Neonatal [Neonatal Period]) – Safety Population (Cumulative Data) [Excludes Congenital Anomalies]**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	AN (study)	Event	Time after dose/age (Outcome)
Others (Cont.)					
Malnutrition	42276 (015)	328d postdose 2/40d (R)	Constipation	46132 (015)	267 d postdose 3/21 d (R)
Bhemolytic strep infection	41848 (015)	393d postdose 3/1d (R)	Convulsions (Sib with convulsions)	24801 (011)	25 months postdose 3 placebo/4 days of age (R)
UTI	45515 (015)	594 d postdose 3/16 d (R)			
Clavicle fracture	48735 (015)	262 d postdose 3/day 1 (R)			
Omphalitis	24090 (011)	497 d postdose 3/1 d(R)			

[infant in more than one category]
*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocols 011, 012, and 015, the entire study period includes visits from Day 1 through 11-Nov-2005.
**Infant has SAE in post-neonatal period as well.
***Potentially Exposed = mother received study material and baby was born at any time after vaccination
R=Recovered
F=Fatal
C=Continuing
Source: Summary of Safety, Appendix 2.7.4:44, p. 920-934, 3/8/06 and p. 465-466

In the neonatal period and post-neonatal period (excluding infants who were breastfeeding), there were 14 infants in the Gardasil group with a respiratory event and 13 infants with a respiratory event in the placebo group. (Note: The number of infants with any respiratory diagnosis were counted from Appendix 2.7.4:44, p. 920-934, Summary of Clinical Safety [3/8/06]; from Appendix 2.7.4:48, p. 958-964, Summary of Clinical Safety [3/8/06]; and from Appendix 2.7.4:26, p. 465-466, Summary of Clinical Safety [3/8/06]). There were 2 children who died from SIDS in the Gardasil group: one at 160 days of age (463 days postdose 3) and one at app. 5 months of age (16 months postdose 3). There was no apparent temporal relationship between these events and receipt of the study vaccine by the mother.

TABLE 310
Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to Test Product – Entire Study Period* (Systemic-Other [Outside Neonatal Period]) – Safety Population (Cumulative Data)**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Respiratory Events					
Bronchiolitis and tracheomalacia, Bronchilolitia and dehydration	25142** (011)	676 d postdose 3/162 d (R)	Bronchiolitis	20490 (011)	387 d postdose 3/58 d **(F)**
Bronchiolitis	31812 (012)	386 d postdose 2/47 d (R)	Asthma, bronchopneumonia	20516** (011)	736 d postdose 3/351 d (R) 864 d postdose 3/484 d (R)
Bronchospasam	42378 (015)	785 d postdose 3/127 d (R)	Pneumonia (with arthropod sting)	25191 (011)	338 d postdose 3/370 d (R)
Pneumonia Bronchiolitis	45967 (015)	719 d postdose 3/72 d (R)	Pneumonia	25328 (011)	775 d postdose 2/420 d (R)
Pneumonia, bacterial	49759 (015)	650 d postdose 3/293 d (R)	Pneumonia Bronchiolitis Anemia	24864 (011)	575 d postdose 3/153 d (R)
Bronchitis	[24636] (011)	27 months postdose 3 Gardasil and 15 months postdose 3 hep B (R)	Pneumonia	45950 (015)	862 d postdose 3/85 d **(F)**
Bronchiolitis (with diarrhea)	32138** (012)	30 and 31 months postdose 3 gardasil/1 month and 2 months of age (R)	Pneumonia	49884 (015)	540 d postdose 3/89 d **(F)**
Pneumonia OM with decreased hearing (Mother with preeclampsia and oligohydramnios)	56349 (015)	20 months postdose 3/11 months of age (R) for pneumonia, decreased hearing resolving	Bronchiolitis	57306 (015)	747 d postdose 3/217 d (R)

TABLE 310 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to Test Product – Entire Study Period* (Systemic-Other [Outside Neonatal Period]) – Safety Population (Cumulative Data)**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Respiratory Events (Cont.)					
Pneumonia	24642 (011)	27 months postdose 3 Gardasil and 15 months postdose 2 Hep B (breast fed) (R)	Pneumonia, bacterial	46400 (015)	326 d postdose 3/52 d (R)
			Pneumonia	55448 (015)	744 d postdose 3/279 d (R)
			Bronchiolitis Bronchiolitis With diarrhea	54827 (015)	473 d postdose 3 582 d postdose 3 539 d postdose 3
			Bronchiolitis	48751 (015)	28-29 months postdose 3 placebo/10-11 months of age (R)
			Bronchopneumonia	45815 (015)	17 months postdose 3 placebo/5 months of age (R)
GI					
Viral diarrhea	31812 (015)	877 d postdose 3/311d (R)	Vomiting, diarrhea	25235 (011)	177 d postdose 3/215 d (R)
GE reflux	43173** (015)	24 months postdose 3/1 month of age (R)	Rotavirus Gastroenteritis	42192 (015)	729 d postdose 3/319 d (R)
GE reflux	43436 (015)	19 months postdose 3 Gardasil/8 months of age (R)	Diarrhea, vomiting	56535 (015)	433 d postdose 3/475 d (R)

TABLE 310 [Cont.] Protocols 013, 015, 016: Listing of SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to Test Product – Entire Study Period* (Systemic-Other [Outside Neonatal Period]) – Safety Population (Cumulative Data)**

Gardasil			Placebo		
Event	AN (study)	Time after dose/age (Outcome)	Event	AN	Time after dose/age (Outcome)
Other					
SIDS	41768 (015)	463 d postdose 3/160 d **(F)**	Febrile convulsion	44194 (015)	714 d postdose 3/316 d (R)
SIDS (previous E. coli infection, GE reflux, sleep apnea)	57822** (015)	16 months postdose 3 Gardasil)/5 months of age [one ot twins] **(F)**			
Death	57031 (015)	505 d postdose 3/44d **(F)**	Fetal arrhythmia	43552 (015)	830 d postdose 3/-4 d (R)
Nephrolithiasis	24085 (011)	703 d postdose 3/417 d (R)	Tonsillitis	24628 (011)	693 d postdose 3/425 d (R)
Viral meningitis	[24636] (011)	471 d postdose 3/183 d (R)	UTI	47866 (015)	514 d postdose 2/73 d (R)
Pyrexia	43303 (015)	514 d postdose 3/139 d (R)	Viral meningitis Bronchostenosis	47758 (015)	429 d postdose 3/138d (R) 30 months postdose 3 placebo/14 months of age (R)
Otitis media	45531 (015)	649 days postdose 3/335 d (R)	Burn with assoc. sepsis, shock (also with hip dysplasia) Pyelonephritis, Cholelithiasis	49420 (015)	703 d postdose 3/335-346 d (C) 27 months postdose 3 placebo/15 months of age (R)
OM, recurrent (Mother with dystocia)	24597 (011)	29 months postdose 3 Gardasil and 13 months postdose 3 Hep B/21 months of age (R)			
Skull fracture	46564 (015)	785 d postdose 3/127 d (R)	Febrile convulsion	44194 (015)	714 d postdose 3/316 d (R)
			Measles, exanthema subitum, hand foot mouth disease	48185 (015)	2 months, 7 months, and 10 months of age (R)
			Dengue fever, bronchiolitis	32025 (012)	30 months postdose 3 placebo/4 months of age (R)

*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocols 011, 012, and 015, the entire study period includes visits from Day 1 through 11-Nov-2005.
**Infant has SAE in neonatal period as well.
***Potentially Exposed = mother received study material and baby was born at any time after vaccination
R=Recovered
F=Fatal
C=Continuing
Source: Summary of Clinical Safety, Appendix 2.7,4:48, p. 958-64, 3/8/06 and SUR Cutoff Date* Through January 25, 2006 [*SUR Cutoff Date for Protocol 007 EXT was 11/30/05 and for the other studies was 11/11/05.]

The sponsor also presented in a list and with WAES reports for other SAEs in infants who were born to subjects in the study through 1/25/06. Although listed as receiving blinded material, the study material received by each subject was located in the original BLA datasets (vacc). This information was added to the tables above (either neonatal table or post-neonatal table as appropriate). Cases of congenital anomalies were added in text below the congenital anomaly table. (See Table 307 and text that follows).
Overall, there were deaths of 7 infants whose mothers were potentially exposed to Gardasil and 7 infants whose mothers were potentially exposed to placebo. (This total includes the one infant with a congenital anomaly and died of pneumonia who was breastfeeding.) Table 311 below presents the infants who died with causes for each and days postvaccination in the mother.

TABLE 311
Protocols 007, 013, 015, 016: Deaths in Infants Potentially Exposed* to Study Material During Follow-up of Phase III studies

Gardasil			Placebo		
Event	AN	Time after dose/age	Event	AN	Time after dose/age
Congenital Anomalies					
Heart disease congenital, duodenal atresia, trisomy 21	47851	EDCn =33/postdose 1 Time of event = 304 days postdose 1 (1 day age)	Amniotic band syndrome	40330	EDCn = 343/postdose 3; Time to event = 469 days postdose 3 (stillborn)
Anomalous pulmonary venous connection (with pneumonia)	56355	EDCn = 57/postdose 2; Time to event = 407 days postdose 2 (app. 10 wks. Age)	Congenital anomaly	46561	EDCn = 498/postdose 3 Time to event = 659 days postdose 3 (stillborn)
Low set ears, limb malformation	24836	EDCn = 285/postdose 3; Time to event = 482 days postdose 3 (1 day age)	(Right Atrial Neoplasm)	24923	Time of event =17 months/postdose 3 (+ Hep B) (3 days of age)
Systemic Neonatal					
With prematurity, fetal growth retardation, bronchiolitis	[54184] (015)	Time of event = 270-298 d postdose 3/1d-28 d (1 day of age)	Prematurity	25312 (011)	Time of event = 643 d postdose 3/1d of age
Outside Neonatal					
SIDS (previous E. coli infection, GE reflux, sleep apnea)	57822** (015)	Time of event = 16 months postdose 3 Gardasil)/5 months of age [one ot twins]	Bronchiolitis	20490 (011)	Time of event = 387 d postdose 3/58 d of age
SIDS	41768 (015)	Time of event = 463 d postdose 3/160 d of age	Pneumonia	45950 (015)	Time of event = 862 d postdose 3/85 d of age
Death (information not available)	57031 (015)	Time of event = 505 d postdose 3/44d of age	Pneumonia	49884 (015)	Time of event = 540 d postdose 3/89 d of age
TOTAL		**7**	**TOTAL**		**7**

* Potentially Exposed = mother received study material and baby was born at any time after vaccination
Source: Tables for infants deaths in this review

Vaccination During Lactation/Subjects who were Breast Feeding during Vaccination Period

- The adverse event experience of mothers who were breast feeding was comparable to the general safety population. (Source: Table 2.7.4:32, p. 183-4; Appendix 2.7.4:191, p. 1061-2; Appendix 2.7.4:192, p. 1063-72; not shown here)
- There appeared to be a higher proportion of subjects in both the Gardasil and placebo groups with a low grade T (app. 20-21% in either group). (Source: Appendix 2.7.4:193, p. 1073, not shown here)
- 3 Gardasil recipients and 6 placebo recipients experienced an SAE. There was no apparent difference between the groups.

TABLE 312
SAEs of Subjects During Breast Feeding/Lactation with Gardasil

AN (Study)	AE	Age	Days postdose	Duration of AE	Outcome
45930 (015)	Appendicitis	23 F	42 days postdose 2	3 days	Recovered
45935 (015)	Pneumonia	19 F	5 days postdose 1	11 days	Recovered
45992 (015)	Cholelithiasis	23 F	3 days postdose 2	6 days	Recovered

Source: Appendix 2.7.4:194, p. 1074-5

In the placebo group, the 6 SAEs included anaphylactic reaction (12 days postdose 1); PID (25 days postdose 1); pyelonephritis (7 days postdose 2); gastritis (43 days postdose 2); pneumonia (14 days postdose 1); and vaginal laceration (7 days postdose 3).

SAEs in Infants whose mothers received study material during the breastfeeding period
The SAEs reported in infants who were breastfeeding and were potentially exposed to the study product from mothers who received study material during the breastfeeding period were reported. Overall, 17 and 9 infants in the Gardasil and placebo groups had an SAE (3.4% and 1.8% of the total number of subjects). For the Gardasil group, there were 23 SAEs in 17 infants. These SAEs included the following: 12 were respiratory infections, 5 were gastroenteritis and diarrhea, 1 each of bronchial obstruction, asthma, cellulitis, dehydration, head injury, and anomalous pulmonary venous return. Of 9 infants in the placebo group with an SAE, 4 had respiratory infections, 2 had gastroenteritis, 1 had an unspecified viral illness, 1 had asthma, and 1 had a febrile convulsion. The interval between vaccination of the mother and the respiratory events in the infants varied from 12-231 days in the 17 infants whose mothers received Gardasil while breastfeeding, and from 3-145 days in the infants whose mothers received placebo while breastfeeding. 6 cases occurred within 30 days after vaccination with Gardasil and 2 occurred within 30 days with placebo. Neither Gardasil nor anti-HPV antibody excretion in milk was specifically studied.

TABLE 313
Protocols 013, 015, 016: SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed to Test Product**
(Entire Study Period-Lactation*) Safety Population

Maternal AN (Study)	AE	Infant Age at AE	Days postdose	Duration of AE	Outcome
56355 (015)	Pneumonia (severe) Anomalous pulmonary venous malformation (severe) [EDCn 57 days postdose 2 see congenital anomalies]	69 days 71 days	19 days postdose 3 Gardasil 21 days postdose 3 Gardasil	19 days 21 days	Fatal
47942 (015)	Bronchopneumonia (moderate)	91 days	12 days postdose 1 Gardasil)	11 days	Recovered
60574 (016)	Pneumonia (severe)	277 days	20 days postdose 2 Gardasil	5 days	Recovered
24012 (011)	Bronchitis (moderate)	662 days	22 postdose 3 Gardasil + hep B placebo	146 days	Recovered
57048 (015)	Asthma (severe) Pneumonia (severe)	589 days	24 days postdose 3 Gardasil	8 days	Recovered
56572 (015)	Pneumonia (severe)	116 days	29 days postdose 1 Gardasil	8 days	Recovered
47369 (015)	URI (severe) Gastroenteritis (severe) Pneumonia (severe)	334 days 338 days 338 days	44 days postdose 1 Gardasil 48 days post above	20 days 16 days 16 days	Recovered Recovered
33654 (012)	Bronchiolitis (moderate)	305 days	112 days postdose 2 Gardasil	10 days	Recovered
47857 (015)	Pneumonia (moderate)	529 days	129 days postdose 2 gardasil	13 days	Recovered
32536 (012)	Bronchiolitis (moderate)	261 days	150 days postdose 3 Gardasil	3 days	Recovered
20420 (011)	Bronchial obstruction (severe) Diarrhea (severe)	201 days	155 days posdose 3 Gardasil + hep B vaccine	7 days 7 days	Recovered
25205 (011)	Pneumonia (severe) Gastroenteritis (moderate)	337 days 401 days	167 days postdose 3 Gardasil + hep B placebo 231 days post above	13 days 1 day	Recovered Recovered
31307 (012)	Cellulitis (moderate)	203 days	84 days postdose 2 Gardasil	12 days	Recovered
42699 (015)	Gastroenteritis (severe)	718 days	38 Days postdose 2 Gardasil	8 days	Recovered
56031 (015)	Head injury (severe)	346 days	23 days postdose 3 Gardasil	3 days	Recovered
47862 (015)	Dehydration (moderate)	263 days	201 days postdose 3 Gardasil	2 days	Recovered
56732 (015)	Diarrhea (moderate)	576 days	126 days postdose 3 Gardasil	3 days	Recovered

*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocol s 011 and 012, the entire study period includes Day 1 through the primary fixed case analysis for Protocol 013 (15-Jul-2005). For Protocol 015, the entire study period includes Day 1 through the primary fixed case analysis (10-Jun-2005).

** Potentially Exposed = mother received study material and baby was born at any time after vaccination

Source: From Appendix 2.7.4:195, p. 1076-9, Original BLA

TABLE 314
Protocols 013, 015, and 016: SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed to Placebo**
(Entire Study Period-Lactation) Safety Population

Maternal AN (Study)	AE	Infant Age at AE	Days postdose	Duration of AE	Outcome
25169 (011)	Pneumonia (moderate)	302 d	3 d postdose 2	3 days	Recovered
47415 (015)	Bronchiolitis (moderate)	233 d	25 days postdose 3	8 days	Recovered
47374 (015)	Asthma (severe)	369 d	46 days postdose 1	2 days	Recovered
20442 (011)	Bronchopneumonia (moderate)	189 d	90d postdose 2	16 days	Recovered
54213 (015)	Pneumonia (mild)	209 d	135 days postdose 2	24 hours	Recovered
24639 (011)	Viral infection (moderate)	543 d	93 d postdose 2	3 days	Recovered
42394 (015)	Gastroenteritis (severe)	374 d	16 days postdose 3	2 days	Recovered
54218 (015)	Gastroenteritis (severe)	407 d	107 days postdose 2	2 days	Recovered
46022 (015)	Febrile convulsion (post wheezing with fever)	477 d	36 days postdose 3	12 days	Recovered

*For Protocol 016, the entire study period includes Day 1 through the end of the study (Month 12). For Protocol s 011 and 012, the entire study period includes Day 1 through the primary fixed case analysis for Protocol 013 (15-Jul-2005). For Protocol 015, the entire study period includes Day 1 through the primary fixed case analysis (10-Jun-2005).
** Potentially Exposed = mother received study material and baby was born at any time after vaccination
Source: From Appendix 2.7.4:195, p. 1076-9, original BLA

TABLE 315
Protocols 013, 015, and 016: SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed to Test Product**
(Entire Study Period-Lactation) Safety Population

Event	**Gardasil** N=500	**Placebo** N=495
Respiratory Infections	12	4 [6]*
Gastroenteritis/Diarrhea	5	2
Asthma	1	1
Bronchial Obstruction	1	0
Cellulitis	1	0
Dehydration	1	0
Head Injury	1	0
Anomalous pulmonary venous return	1	0
Unspecified Viral Infection	0	1
Febrile Convulsion	0	1

Source: Summary of Clinical Safety, p. 181-2 and Appendix 2.7.4:195, p. 1076-9
*see text below
** Potentially Exposed = mother received study material and baby was born at any time after vaccination

TABLE 316
Protocols 013, 015, and 016: SAEs Reported in Infants of Vaccinated Subjects who were Potentially Exposed* to Test Product
(Entire Study Period-Systemic Neonatal and Systemic Other) Safety Population
(Excludes Infants who were Breastfeeding)

Event	Gardasil N= at least 621 + 3 live births	Placebo N=at least 611 + 4 live births
Respiratory Infections	14	13
Neonatal Respiratory Distress Syndrome	2**	5

*Potentially Exposed=infant born to mother who received study material at any time during study, excludes children who were breastfeeding.
**One infant with congenital anomaly
Source: Summary of Clinical Safety, Table 2.7.4:44, p. 920-934 and
Table 2.7.4:48, p. 958-964.

The SAEs for the infants who were breastfeeding in each group were reviewed from the Case Report Forms. All subjects in both treatment groups were from South America. In the overall safety group (which excludes subjects who were breastfeeding), there was a similar number of infants with a respiratory events in the placebo (13) group compared to the Gardasil group (14), although there were more infants with neonatal respiratory distress syndrome events in the placebo group as compared to the Gardasil group (5 vs. 2). The subjects in the "overall safety groups" did not appear to overlap with those in the breastfeeding group.

Infants of Gardasil Recipients who were Breastfeeding (See Table 314)
Most of the mothers received vaccine at other times without negative impact on the infants, so it is not clear that there is a relationship between breastfeeding and respiratory events in infants of mothers who were breastfeeding.

- AN 56355 (015-031, Mexico): The child develeped pneumonia 19 days after the mother received dose 3, but was soon diagnosed with a congenital anomaly (anomalous pulmonary venous malformation) that may have contributed to the development of pneumonia.
- AN 47942 (015-070, Brazil): The subject received 2 additional doses of vaccine without further AE in the infant.
- AN 60574 (016-0039, Brazil): The subject was breastfeeding on enrollment. There was no AE in the infant after doses 1 and 3.
- AN 24012 (011-015, Brazil): This subject received doses 1 and 2 without AE in the infant. The duration of the bronchitis was prolonged, but the child did not require hospitalization.
- AN 57048 (015-021, Peru): The subject was breastfeeding at enrollment, and there was no AE in the infant after doses 1 and 3. The mother had a history of asthma as well.
- AN 56572 (015-021, Peru): The subject received doses 2 and 3 while breastfeeding without AE in the infant.

- AN 47369 (015-021, Peru): The subject was breastfeeding on enrollment, and received doses 2 and 3 without AE in the infant.
- AN 33654 (012-040, Colombia): The subject was breastfeeding on enrollment, and received doses 1 and 3 without AE in the infant.
- AN 47857 (015-041, Colombia): The subject was breastfeeding after doses 1 and 3 without AE in the infant.
- AN 32536 (012-041, Colombia): This subject was not pregnant on enrollment. She received the first 2 doses of HPV+Hepatitis B vaccine on 1/8/03 and 2/19/03. She became pregnant and the child was born ---------. The child became ill 3/15/04, and she then received the third doses of vaccine 5/14/04.
- AN 20420 (011-021, Peru): This subject received the first 2 doses on 9/27/02 and 12/2/02 before becoming pregnant. She delivered a baby -------. She began breastfeeding. The child developed pneumonia and gastroenteritis 155 days postdose 3.
- AN 25205 (011-015, Brazil): This subject received dose 1 on 3/3/03. She became pregnant and delivered the baby --------. She recived dose 2 without problem, and received dose 3 on 4/24/04. The child became ill 10/13/04.
- AN 31307 (012-040, Colombia): This subject was breastfeeding on enrollment. She received doses 1 and 3 without AE in the infant.
- AN 42699 (015-021, Peru): This subject was breastfeeding on enrollment. She received doses 1 without problem. She received dose 2 on 12/26/02, and the child developed gastroenteritis 2/1/03. She stopped breastfeeding before the 3rd dose.
- AN 47862 (015-041, Bogota): This subject received dose 1 on 2/4/03 and dose 2 on 3/21/03. The subject became pregnant and the baby was born -------- with neonatal persistent circulation and premature. The subject began breastfeeding with the birth of the baby, and received dose 3 on 4/23/04. On 11/9/04, the baby developed dehydration due to diarrhea.
- AN 56732 (015-0042, Colombia): The subject was breastfeeding on enrollment, and there were no AEs after doses and 2. The subject received dose 3 on 8/12/03, and the SAE occurred 12/15/03.

[The child with the head injury fell out of bed and there is no obvious connection to vaccination.]

<u>Infants of Placebo Recipients who were Breastfeeding: (See Table 315 also).</u>

- AN 47374 (015-021, Peru): The subject was breastfeeding on enrollment. There were no additional AEs in the infant after doses 2 and 3.
- AN 20442 (011-013, Brazil): The subject was breastfeeding on enrollment. There were no AEs after doses 1 or 3.
- AN 54213 (015-070, Brazil): The subject was breastfeeding on enrollment and there was no AE after dose 1. The subject stopped breastfeeding after the mild pneumonia which occurred 135 days after dose 2.
- AN 46022 (015-022, Mexico): This subject was breastfeeding on enrollment. There were no AEs after doses 1 and 2. It is noted that the child presented with wheezing and fever at the time of the febrile seizure, so there may have been a respiratory infection which was the cause of the fever. No CXR was reported, however.

- AN 24639 (011-018, Brazil): The subject was breastfeeding on enrollment. There were no AEs after doses 1 and 3.
- AN 42394 (015-021, Peru): This subject was breastfeeding on enrollment, and received doses 1 and 2 without AE in the infant.
- AN 54218 (015-021, Peru): The subject was breastfeeding on enrollment, and had no AE after doses 1 and 3.

Reviewer's Comment: It is acknowledged that the sponsor provided close follow-up of infants of mothers who received the vaccine, and this is not usually provided in clinical studies. Because of the small number of events, it is difficult to draw strong safety conclusions. In the majority of cases, similar adverse events did not occur after other doses of the same study material, and the times to event after exposure were variable.

10.4 Other Safety Findings

10.4.1 ADR Incidence Tables (Local and Systemic Events)

Injection site AEs

The proportion of subjects reporting an injection-site adverse experience within 5 days of any vaccination was higher in subjects who received Gardasil (83%) was higher compared with subjects who received aluminum-containing placebo (77%) or non-aluminum-containing placebo (50%).

Overall, the proportions of subjects reporting any injection site AE in the 5 days after vaccination were higher postdose 1 as compared to postdose 2 or 3.

Comparison of the overall Gardasil group and overall alum placebo group to non-alum saline placebo is included in Tables 317 and 318 below. The direct comparison of AEs that occurred in vaccine recipients and saline placebo recipients is included in the review of Study 018, and in that study, there was also a higher incidence of injection site AEs in the Gardasil group as compared to saline placebo.

TABLE 317
Protocols 007, 011, 012, 013, 015, 016, and 018: Number (%) of subjects with Injection Site AEs ≥ 1% in Days 1-5 after any Vaccination Visit in Detailed Safety Population

	Gardasil N=6160	Placebo (Non-alum) N=594	Placebo (Alum) N=3470
Subjects with follow-up	6069	584	3410
Subjects with one or more injection site AE	5030 (82.9%)	289 (49.5%)	2638 (77.4%)
Injection Site Pain	4935 (81.3%)	265 (45.4%)	2572 (75.4%)
Injection Site Swelling	1469 (24.2%)	45 (7.7%)	540 (15.8%)
Injection Site Erythema	1432 (23.6%)	77 (13.2%)	629 (18.4%)
Injection site hemorrhage	197 (3.2%)	15 (2.6%)	133 (3.9%)
Injection site Pruritus	167 (2.8%)	5 (0.9%)	97 (2.8%)
Injection site paresthesias	22 (0.4%)	10 (1.7%)	5 (0.1%)

Source: From Table 2.7.4:13, p. 90-1 and Appendix 2.7.4:41, p. 449-51

TABLE 318
Protocols 007, 013, 015, 016, and 018: Number (%) of Subjects with Injection Site AEs ≥ 1% in Days 1-5 after Dose 1, Dose 2, and Dose 3 in Detailed Safety Population

	Gardasil N=6160 total	Placebo (Non-alum) N=594 total	Placebo (Alum) N=3470 total
Post Dose 1			
Subjects with follow-up	6068	584	3410
Subjects with one or more injection site AE	3874 (63.8%)	196 (33.6%)	2068 (60.6%)
Subjects with injection site pain	3702 (61.0%)	180 (30.8%)	1943 (57.0%)
Subjects with injection site swelling	568 (9.4%)	27 (4.6%)	281 (8.2%)
Subjects with injection site erythema	536 (8.8%)	42 (7.2%)	333 (9.8%)
Subjects with Injection site hemorrhage	86 (1.4%)	8 (1.4%)	64 (1.9%)
Subjects with Injection site pruritus	64 (1.1%)	3 (0.5%)	54 (1.6%)
Post Dose 2			
Subjects with follow-up	5960	5634	1684
Subjects with one or more injection site AE	3542 (59.4%)	130 (23.0%)	1684 (50.3%)
Subjects with injection site pain	3406 (57.1%)	115 (20.4%)	1603 (47.8%)
Subjects with injection site swelling	719 (12.1%)	13 (2.3%)	250 (7.5%)
Subjects with injection site erythema	677 (11.4%)	31 (5.5%)	282 (8.4%)
Subjects with Injection site hemorrhage	61 (1.0%)	6 (1.1%)	44 (1.3%)
Subjects with Injection site pruritus	62 (1.0%)	2 (0.4%)	22 (0.7%)
Post Dose 3			
Subjects with follow-up	5837	559	3296
Subjects with one or more injection site AE	3514 (60.2%)	137 (24.5%)	1689 (51.2%)
Subjects with injection site pain	3405 (58.3%)	124 (22.2%)	1633 (49.5%)
Subjects with injection site swelling	842 (14.4%)	19 (3.4%)	249 (7.6%)
Subjects with injection site erythema	808 (13.8%)	30 (5.4%)	293 (8.9%)
Subjects with Injection site hemorrhage	69 (1.2%)	1 (0.2%)	35 (1.1%)
Subjects with Injection site pruritus	67 (1.1%)	1 (0.2%)	30 (0.9%)

Source: From Appendices 2.7.4:42, 43, 44, p. 452-6

Intensity of injection site AEs in the 5 days after any vaccination

For most subjects, the maximum intensity rating of injection-site adverse experiences was mild or moderate. The percentages of subjects who developed injection site adverse events which were rated as moderate or severe were slightly higher in the group that received Gardasil (26.1% moderate, 4.5% severe) than in the combined placebo group (18.1% moderate, 1.9% severe). (See Table 319 below)

TABLE 319
Protocols 007, 013, 015, 016, 018: Number (%) of Subjects Who Reported Injection Site Adverse Events by Maximum Intensity Rating (Days 1-5 Following Any Vaccination Visit) in the Detailed Safety Population

	Gardasil N=6160	Placebo N=4064
Subjects with follow-up	6069	3994
Subjects with Injection Site AEs	5030 (82.9%)	2927 (73.3%)
Mild	3162 (52.1%)	2125 (53.2%)
Moderate	1586 (26.1%)	724 (18.1%)
Severe	271 (4.5%)	76 (1.9%)
Unknown	11 (0.2%)	2 (0.1%)

Percentages calculated based on number of subjects with follow-up.
N=Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the given column.
Source: Appendix 2.7.4:45, p. 458, summary of clinical safety

Few subjects (5 GARDASIL recipients and 3 placebo recipients) discontinued from their respective studies due to injection-site adverse experiences.

A comparison of the number and percentage of subjects who reported severe injection site adverse experiences within 5 days following any vaccination visit between vaccination groups is shown in Table 320 below. There appears to be a significantly higher rate of severe injection site AEs within 5 days after receipt of Gardasil as compared to receipt of placebo (alum and non-alum combined).

TABLE 320
Protocols 007, 013, 015, 016, and 018: Comparison of Vaccination Groups with Respect to the Number (%) of Subjects Who Reported Severe Injection Site Adverse Events (Days 1-5 Following Any Vaccination Visit) in the Detailed Safety Population

	Gardasil N=6160	Placebo N=4064	Risk Difference (Gardasil minus Placebo) (95% CI)
Subjects with follow-up	6069	3994	
Subjects with severe Injection Site AEs Days 1-5 after any vaccination visit	271 (4.5%)	76 (1.9%)	2.6 (1.9, 3.2)

Percentages calculated based on the number of subjects with follow-up.
N=number of subjects who received dose 1, 2, or 3 of only the clinical material listed in the given column
Source: Appendix 2.7.4:47, p. 460

Systemic AEs

The most commonly reported systemic adverse experiences were headache, pyrexia, and nausea. The proportions of subjects who reported a systemic adverse experience were comparable between the 2 Gardasil and combined placebo group. (See Table 321 below).

TABLE 321
Protocols 007, 013, 015, 016, and 018: Number (%) of Subjects with Systemic AEs ≥ 1% in Days 1-15 after any Vaccination Visit in Detailed Safety Population

	Gardasil N=6160	Placebo N=4064
Subjects with follow-up	6069	3994
Subjects with one or more systemic AE	3591 (59.2%)	2414 (60.4%)
Headache	1602 (26.4%)	1101 (27.6%)
Pyrexia	782 (12.9%)	440 (11.0%)
Nausea	370 (6.1%)	251 (6.3%)
Diarrhea	224 (3.7%)	144 (3.6%)
Nasopharyngitis	353 (5.8%)	245 (6.1%)
Pharyngolaryngeal Pain	266 (4.4%)	190 (4.8%)
Dizziness	214 (3.5%)	142 (3.6%)
Skin Disorder	210 (3.5%)	143 (3.6%)
Abdominal Pain upper	193 (3.2%)	136 (3.4%)
Influenza	192 (3.2%)	154 (3.9%)
Dysmenorrhea	178 (2.9%)	152 (3.8%)
Abdominal Pain	157 (2.6%)	115 (2.9%)
Fatigue	156 (2.6%)	154 (3.9%)
Vomiting	147 (2.4%)	82 (2.1%)
Injury, poisoning and procedural complications	143 (2.4%)	85 (2.1%)
Myalgia	119 (2.0%)	81 (2.0%)
Pain in extremity	118 (1.9%)	95 (2.4%)
Cough	117 (1.9%)	63 (1.6%)
Back Pain	116 (1.9%)	99 (2.5%)
URI	93 (1.5%)	59 (1.5%)
Toothache	78 (1.3%)	53 (1.3%)
Malaise	75 (1.2%)	46 (1.2%)
Arthralgia	74 (1.2%)	39 (1.0%)
Ear and Labyrinth Disorders	70 (1.2%)	38 (1.0%)
Nasal congestion	67 (1.1%)	39 (1.0%)
Insomnia	60 (1.0%)	34 (0.9%)
Eye Disorders	54 (0.9%)	49 (1.2%)
Pharyngitis	50 (0.8%)	40 (1.0%)
Somnolence	49 (0.8%)	43 (1.1%)

Source: From Table 2.7.4:14, p. 93-97

Comparison of systemic AEs between Gardasil and saline placebo

Systemic AEs were compared in the Gardasil group and saline placebo in Study 018, and the rates of systemic adverse events for 9-15 year old children in Protocol 018 were similar in the Gardasil and placebo groups. (See review of Study 018).

Only 9-15 year old children received the non-alum placebo. When these subjects were compared with all Gardasil recipients in the Detailed Safety group, there were higher proportions of Gardasil recipients with headache, pyrexia, nausea, diarrhea, and nasopharyngitis and pharyngolaryngeal pain. 9-15 year old children who received Gardasil overall had lower proportions of adverse events compared to 16-23 year old subjects (as noted earlier in Study 016).

TABLE 322
Number (%) of Subjects with Systemic AEs in Days 1 -15 After Any Vaccination Visit: Gardasil Recipients in Detailed Safety Cohort Overall (Protocols 007, 013, 015, 016, 018) Compared to Non-Alum Placebo Recipients in Protocol 018

	Gardasil N=6160	Non-Alum Placebo N=594
Subjects with follow-up	6069	584
Subjects with one or more systemic AE	3591 (59.2%)	260 (44.5%)
Headache	1602 (26.4%)	110 (18.8%)
Pyrexia	782 (12.9%)	32 (5.5%)
Nausea	370 (6.1%)	22 (3.8%)
Diarrhea	224 (3.7%)	21 (3.6%)
Nasopharyngitis	353 (5.8%)	22 (3.8%)
Pharyngolaryngeal Pain	266 (4.4%)	24 (4.1%)
Dizziness	214 (3.5%)	9 (1.5%)
Skin Disorder	210 (3.5%)	20 (3.4%)
Abdominal Pain upper	193 (3.2%)	17 (2.9%)
Influenza	192 (3.2%)	12 (2.1%)
Dysmenorrhea	178 (2.9%)	7 (1.2%)
Abdominal Pain	157 (2.6%)	12 (2.1%)
Fatigue	156 (2.6%)	7 (1.2%)
Vomiting	147 (2.4%)	18 (3.1%)
Injury, poisoning and procedural complications	143 (2.4%)	15 (2.6%)
Myalgia	119 (2.0%)	10 (1.7%)
Pain in extremity	118 (1.9%)	14 (2.4%)
Cough	117 (1.9%)	14 (2.4%)
Back Pain	116 (1.9%)	2 (0.3%)
URI	93 (1.5%)	9 (1.5%)
Toothache	78 (1.3%)	2 (0.3%)
Malaise	75 (1.2%)	2 (0.3%)
Arthralgia	74 (1.2%)	9 (1.5%)
Ear and Labyrinth Disorders	70 (1.2%)	7 (1.2%)
Nasal congestion	67 (1.1%)	9 (1.5%)
Insomnia	60 (1.0%)	2 (0.3%)
Eye Disorders	54 (0.9%)	3 (0.5%)
Pharyngitis	50 (0.8%)	5 (0.9%)
Somnolence	49 (0.8%)	3 (0.5%)

Source: From Table 2.7.4:14, p. 93-97, Protocol 018v2, Table 8-11, p. 157-8, Table 11-58, p. 312-325

Elevated Temperature

Most subjects had a maximum T < 100 deg F (< 37.8 deg C) oral equivalent. The proportion of subjects who reported a fever was slightly higher among Gardasil recipients

as compared to placebo recipients. (See Table 323 below). However, most were low grade. Two placebo recipients discontinued from their studies due to pyrexia.

TABLE 323
Protocols 007, 013, 015, 016 and 018: Number (%) of Subjects with Elevated Temperatures (Days 1-5 Following Any Vaccination Visit) in the Detailed Safety Population

	Gardasil N=6160	Placebo N=4064
Subjects with follow-up	6040	3981
Maximum T (Oral)		
<37.8 °C (< 100 °F) or normal	5354 (88.6%)	3597 (90.4%)
≥ 37.8 °C (≥ 100°F) and < 38.9 °C (< 102 ° F) or abnormal	596 (9.9%)	343 (8,6%)
≥ 38.9 °C (≥ 102°F) and < 39.9 °C (< 103.8 ° F)	76 (1.3%)	34 (0.9%)
≥ 39.9 °C (≥ 103.8°F) and < 40.9 °C (< 105.6 ° F)	12 (0.2%)	4 (0.1%)
≥ 40.9 °C (≥ 105.6°F)	2 (0.03%)	3 (0.1%)

Source: Summary of Clinical Safety, Table 2.7.4:15, p. 99

Overall Clinical AEs in Adult Female Subjects 18-26 years of age
AEs were shown for adult women in the Gardasil group compared to alum placebo group. Table 324 below shows this comparison Days 1-15 after any vaccination visit. The findings are similar to those seen for the overall combined Detailed Safety Population.

The proportion of subjects who reported any AE, and the proportion of subjects who reported an injection site AE were higher in the Gardasil groups compared to placebo group.

The proportions of subjects with a severe AE were similar between the Gardasil (15.7%) and the placebo (14.5%) groups. (Source: Appendix 2.7.4:71, p. 775, not shown here, clinical summary safety). Most of the AEs in both groups were mild to moderate (app. 94%) in severity. (Source: Appendix 2.7.4:72, p. 776, not shown here, clinical summary safety)

The proportions of subjects who reported an SAE and the proportions of subjects who reported a systemic AE were comparable between the two groups.

Discontinuations were uncommon in each group.

TABLE 324
Protocols 007, 013, 015, 016: Clinical AE Summary (Days 1-15 after any vaccination) Detailed Safety Population – Female Subjects 18-26 years of Age at Study Enrollment

	Gardasil N=3697	Placebo N=3269
Subjects with follow-up	3640	3213
Subjects with one or more AE	3370 (92.6%)	2852 (88.8%)
Subjects with one or more IS AE	3166 (87.0%)	2499 (77.8%)
Subjects with one or more systemic AE	1481 (40.7%)	1252 (39.0%)
Subjects with SAEs	26 (0.7%)	22 (0.7%)
Subjects who died	1 (0.03%)	1 (0.03%)
Subjects who discontinued due to AE	5 (0.1%)	6 (0.2%)

Percentages calculated based on subjects with follow-up.
IS AE = injection site AEs
N=number of subjects who received 1, 2, or 3 dose of only the clinical material indicated in the column.
Source: Table 2.7.4:21, p. 131-2, Clinical summary safety

The proportions of subjects with a severe AE were similar between the Gardasil (15.7%) and the placebo (14.5%) groups. (Source: Appendix 2.7.4:71, p. 775, not shown here, clinical summary safety). Most of the AEs in both groups were mild to moderate (app. 94%) in severity. (Source: Appendix 2.7.4:72, p. 776, not shown here, clinical summary safety)

Injection Site AEs in Adult Females 18-26 years of age
In adult women, there was a higher proportion of Gardasil recipients with an injection site AE compared to the placebo recipients, and these included pain, swelling and erythems. The proportion of subjects with injection site hemorraage and pruritus were lower and similar in both treatment groups.

TABLE 325
Protocols 007, 013, 015, 016: Number (%) of subjects with Injection Site AEs (Incidence ≥ 1% in One or More Vaccination Groups Days 1-5 after any Vaccination Visit) – Subjects 18-26 years of age at study enrollment

	Gardasil N=3697	Alum Placebo N=3269
	AEs	AEs
Subjects with follow-up	3640	3213
Subjects with 1+ IS AE	3163 (86.9%)	2497 (77.7%)
Injection site Pain	3116 (85.6%)	2437 (75.8%)
Injection site swelling	924 (25.4%)	507 (15.8%)
Injection site erythema	932 (25.6%)	592 (18.4%)
Injection site hemorrhage	139 (3.8%)	120 (3.7%)
Injection site pruritus	131 (3.6%)	92 (2.9%)

Source: Appendix 2.7.4:73, p. 777-8

A higher proportion of subjects reported a severe injection site reaction in the Gardasil group (4.5%) as compared to the placebo group (2.1%), and a higher proportion of subjects reported an injection site AE that was moderate or severe in the Gardasil group

(33.5%) as compared to the placebo group (21.9%). (Source: Appendix 2.7.4:74, p. 779, not shown here, summary clinical safety)
Most of the injection site AEs were mild to moderate (app. 87-88%) in both groups. (Source: Appendix 2.7.4:75, p. 780, not shown here, clinical summary safety).

Systemic AEs in Adult Females 18-26 years of age
The proportion of subjects in this age group with systemic AEs at Days 1-15 after any vaccination was comparable between the Gardasil (64.5%) and placebo (63.2%) groups.

The most common systemic AEs were headache (30.1% Gardasil, 29.3% placebo) and pyrexia (13.4% Gardasil, 11.5% placebo). Nasopharyngitis was also more commonly seen (7.3% Gardasil, 6.7% placebo). (Source: Appendix 2.7.4:76, p. 781-6, not shown here, Summary of Clinical Safety).

The proportion of subjects with a severe systemic AE was comparable between the two groups (12.6% Gardasil, 12.9% placebo). These percentages were calculated on the number of subjects with follow-up. (Source: Appendix 2.7.4:77, p. 787, not shown here, summary of clinical safety)

Most of the systemic AEs were mild to moderate in intensity in both groups (app. 88% for each group). (Source: Appendix 2.7.4:78, p. 788, not shown here, Summary of Clinical Safety).

Temperatures in Adult Females 18-26 years of age
The proportion of subjects who reported an elevated T was slightly higher in the Gardasil group (12%) as compared to the placebo group (9.9%). Most of these Temperature elevations in both groups were low grade. (See Table 326 below.)

TABLE 326
Protocols 007, 013, 015, 016: Number (%) of Subjects with Elevated T (Days 1-5) after any Vaccination Visit (Detailed Safety Population) – Female Subjects 18-26 years of age at Study Enrollment

	Gardasil N=3697	Placebo N=3269
Subjects with follow-up	3620	3208
Maximum T (Oral)		
<37.8 °C (< 100 °F) or normal	3186 (88.0%)	2890 (90.1%)
≥ 37.8 °C (≥ 100°F) and < 38.9 °C (< 102 ° F) or abnormal	390 (10.8%)	286 (8.9%)
≥ 38.9 °C (≥ 102°F) and < 39.9 °C (< 103.8 ° F)	38 (1.0%)	26 (0.8%)
≥ 39.9 °C (≥ 103.8°F) and < 40.9 °C (< 105.6 ° F)	6 (0.2%)	4 (0.1%)
≥ 40.9 °C (≥ 105.6°F)	0 (0.0%)	2 (0.1%)

Percentages calculated based on number of subjects with follow-up.
Source: Appendix 2.7.4:79, p. 789, Summary of Clinical Safety

Overall Clinical AEs in Females 9-17 years of age

TABLE 327
Protocols 007, 013, 015, 016 and 018: Clinical AE Summary (Days 1-15 after any Vaccination Visit) Detailed Safety Population – Female Subjects 9-17 years of age at Study Enrollment

	Gardasil N=1391	Placebo* N=521
Subjects with follow-up	1372	512
Subjects with one or more AE	1214 (88.5%)	391 (76.4%)
Subjects with one or more IS AE	1111 (81.0%)	303 (59.2%)
Subjects with one or more systemic AE	742 (54.1%)	273 (53.3%)
Subjects with SAEs	7 (0.5%)	4 (0.8%)
Subjects who died	0 (0.0%)	0 (0.0%)
Subjects who discontinued due to AE	2 (0.1%)	0 (0.0%)

Percentages calculated based on subjects with follow-up.
IS AE = injection site AEs
N=number of subjects who received 1, 2, or 3 dose of only the clinical material indicated in the column.
*Placebo includes alum and saline placebo.
Source: Table 2.7.4:22, p. 135-6

The proportion of subjects reporting a moderate or severe AE is higher in the Gardasil group (49.4%) as compared to the placebo group (40.4%). (Source: Appendix 2.7.4:80, p. 790, Summary of Clinical Safety, not shown here) However, most of the AEs reported were mild to moderate in both groups (95.2% Gardasil, 93.5% placebo). (Source: Appendix 2.7.4:81, p. 791. Summary of Clinical Safety, not shown here)

Injection Site AEs in Females 9-17 years of age

There were higher proportion of female subjects 9-17 years of age with an injection site AE (80.8%) compared to saline placebo (51.1%) and alum placebo (71.6%). The proportions of Gardasil recipients with injection site pain, swelling, and erythema were higher compared to the proportions in the placebo group.

TABLE 328
Protocols 007, 013, 015, 016, 018: Number (%) of subjects with Injection Site AEs (Incidence ≥ 1% in One or More Vaccination Groups Days 1-5 after any Vaccination Visit) – Detailed Safety Population:
Female Subjects 9-17 years of age at study enrollment

		Placebo	
	Gardasil N=1391	Non-Alum Placebo N= 320	Alum Placebo N= 201
	AEs	AEs	AEs
Subjects with follow-up	1372	315	197
Subjects with 1+ IS AE	1109 (80.8%)	161 (51.1%)	141 (71.6%)
Injection site Pain	1087 (79.2%)	153 (48.6%)	135 (68.5%)
Injection site swelling	347 (25.3%)	23 (7.3%)	33 (16.8%)
Injection site erythema	304 (22.2%)	38 (12.1%)	37 (18.8%)
Injection site hemorrhage	39 (2.8%)	5 (1.6%)	13 (6.6%)
Injection site pruritus	27 (2.0%)	2 (0.6%)	5 (2.5%)
Injection site paresthesias	10 (0.7%)	8 (2.5%)	0 (0.0%)
Injection site hypersensitivity	4 (0.3%)	0 (0.0%)	3 (1.5%)

Source: Appendix 2.7.4:82, p. 792-3, Summary of clinical safety

The proportion of subjects in the Gardasil group who reported a severe injection site AE (5.2%) was higher than the proportion of subjects in the combined placebo group (1.4%). There was also a higher proportion of subjects in the Gardasil group who had a reported a moderate or severe injection site AE (31%) as compared to the combined placebo group (15.7%). (Source: Appendix 2.7.4:83, p. 794, summary of clinical safety, not shown here)
However, the majority of subjects with follow-up who had an injection site AE reported them to be mild to moderate in both groups. (Source: Appendix 2.7.4:84, p. 795. summary of clinical safety, not shown here)

Systemic AEs in Females 9-17 years of age
The proportions of subjects reporting any systemic AE and the proportions of subjects reporting specific systemic AEs were comparable between the 2 groups (54.1% for Gardasil and 53.3% for placebo). The most common systemic AEs were headache (app. 23% for both groups) and pyrexia (12.2% for Gardasil and 10.0% for placebo). (See Table 329 below).

TABLE 329
Protocols 007, 013, 015, 016, and 018: Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) Detailed Safety Population — Female Subjects 9 to 17 Years of Age at Study Enrollment

	Gardasil N=1391	Placebo* N=521
Subjects with follow-up	1372	512
Subjects with one or more systemic AE	742 (54.1%	273 (53.3%)
Headache	317 (23.1%)	119 (23.2%)
Pyrexia	168 (12.2%)	51 (10.0%)
Nausea	64 (4.7%)	36 (7.0%)
Diarrhea	50 (3.6%)	13 (2.5%)
Nasopharyngitis	54 (3.9%)	21 (4.1%)
Pharyngolaryngeal Pain	54 (3.9%)	22 (4.3%)
Dizziness	36 (2.6%)	19 (3.7%)
Skin Disorder	35 (2.6%)	14 (2.7%)
Abdominal Pain upper	56 (4.1%)	19 (3.7%)
Influenza	29 (2.1%)	18 (3.5%)
Dysmenorrhea	29 (2.1%)	15 (2.9%)
Abdominal Pain	29 (2.1%)	15 (2.9%)
Fatigue	29 (2.1%)	10 (2.0%)
Vomiting	40 (2.9%)	11 (2.1%)
Injury, poisoning and procedural complications	43 (3.1%)	15 (2.9%)
Myalgia	28 (2.0%)	8 (1.6%)
Pain in extremity	28 (2.0%)	15 (2.9%)
Cough	22 (1.6%)	8 (1.6%)
Back Pain	13 (0.9%)	9 (1.8%)
URI	27 (2.0%)	9 (1.8%)
Toothache	15 (1.1%)	5 (1.0%)
Malaise	15 (1.1%)	5 (1.0%)
Arthralgia	25 (1.8%)	6 (1.2%)
Ear and Labyrinth Disorders	22 (1.6%)	6 (1.2%)
Nasal congestion	11 (0.8%)	6 (1.2%)
Pharyngitis	8 (0.6%)	6 (1.2%)

*Placebo = combined placebo.
Source: Appendix 2.7.4:85, p. 796-800, summary of clinical safety, not shown here)

The majority of subjects with a systemic AE reported them to be mild or moderate in intensity in both groups. (Source: Appendix 2.7.4:86, p. 801, not shown here) Of AEs reported, there was a higher frequency of severe AEs in the placebo group (11.1%) as compared to the Gardasil group (7.7%). (See Table 330 below).

TABLE 330
Protocols 007, 013, 015, 016, and 018: Frequency of Intensity Ratings of All Systemic Clinical Adverse Events (Days 1-15 Following Any Vaccination Visit) Detailed Safety Population -
Females Subjects 9-17 Years of Age at Study Enrollment

	Gardasil N=1391	Placebo N=521
Systemic AEs reported	1854	704
Systmeic AEs by Intensity		
Mild	938 (50.6%)	337 (47.9%)
Moderate	757 (40.8%)	279 (39.6%)
Severe	142 (7.7%)	78 (11.1%)
Unknown	17 (0.9%)	10 (1.4%)

Percentages calculated based on number of systemic AEs reported.
N=Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the given column.
Source: Appendix 2.7.4:87, p. 802, summary of clinical safety

The proportions of subjects reporting AEs as mild, moderate or severe were comparable between the groups. (See Table 331 below).

TABLE 331
Protocols 007, 013, 015, 016, and 018: Number (%) of Subjects Who Reported Sstemic Adverse Events by Maximum Intensity Rating (Days 1-15 Following Any Vaccination Visit) Detailed Safety Population -
Females Subjects 9-17 Years of Age at Study Enrollment

	Gardasil N=1391	Placebo N=521
Subjects with follow-up	1372	512
Subjects with Systemic AEs	742 (54.1%)	273 (53.3%)
Mild	293 (21.4%)	100 (19.5%)
Moderate	335 (24.4%)	115 (22.5%)
Severe	101 (7.4%)	52 (10.2%)
Unknown	13 (0.9%)	6 (1..2%)

Percentages calculated based on number of subjects with follow-up.
N=Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the given column.
Source: Appendix 2.7.4:86, p. 801, summary of clinical safety

Temperatures in Females 9-17 years of age
The proportions of subjects who reported an elevated T Days 1 – 5 after any vaccination were comparable between the vaccination groups.

TABLE 332
Protocols 007, 013, 015, 016, and 018: Number (%) of Subjects with Elevated Temperatures (Days 1-5 Following Any Vaccination Visit) Detailed Safety Population- Female Subjects 9-17 Years of Age at Study Enrollment

	Gardasil N=1391	Placebo N=521
Subjects with follow-up	1368	504
Maximum T (Oral)		
<37.8 °C (< 100 °F) or normal	1226 (89.6%)	453 (89.9%)
≥ 37.8 °C (≥ 100°F) and < 38.9 °C (< 102 ° F) or abnormal	120 (8.8%)	44 (8.7%)
≥ 38.9 °C (≥ 102°F) and < 39.9 °C (< 103.8 ° F)	18 (1.3%)	6 (1.2%)
≥ 39.9 °C (≥ 103.8°F) and < 40.9 °C (< 105.6 ° F)	3 (0.2%)	0 (0.0%)
≥ 40.9 °C (≥ 105.6°F)	1 (0.1%)	1 (0.2%)

Percentages calculated based on the number of subjects with follow-up.
All non-oral Ts have been converted to oral equivalent by adding 1 °F to axillary T or subtracting 1°F from rectal T.
N=number of subjects who received 1, 2, or 3 doses of only the clinical material indicated In the given column.
Source: Appendix 2.7.4:88, p. 803, summary of clinical safety

10.4.2 Laboratory Findings, Vital Signs, ECGs, Special Diagnostic Studies: There were no additional laboratory tests, EKGs, special diagnostic studies, or vital sign abnormalities except as noted in the review.

10.4.3 Product-Demographic Interactions (e.g., Age, Gender, etc.)
Adverse events by Race/Ethnicity

The AE profiles for each race/ethnic group (white – 3890 vaccinees and 2491 placebo; black – 354 vaccinees and 272 placebos; Hispanic – 1056 vaccinees and 741 placebos; Asian – 531 vaccinees and 260 placebo recipients) within the Detailed Safety Popualtion were generally similar to the AE profile in the overall Detailed Safety Population. The Hispanic group had a somewhat higher percentage of subjects with a low grade Temperature in both the Gardasil group (13.5%) and placebo group (10.6%) compared to whites (7.5% and 6.7% for Gardasil and placebo recipients), as did the Asian group (14.2% Gardasil and 8.6% placebo). (Source: Appendices 2.7.4:98-117, p. 817-69)

TABLE 333
Protocols 005, 007, 013, 015, 016, 018: Summary of AEs Across Ethnic Groups

	Whites		Blacks		Hispanic		Asian		Other	
	G N=3890	P N=2491	G N=354	P N=272	G N=1056	P N=741	G N=531	P N=260	G N=329	P N=300
Subjects with f/u	3839	2452	341	263	1042	724	527	257	320	298
1+ AE	3473 90.5%	2122 86.5%	283 83%	209 79.5%	953 91.5%	620 85.6%	444 84.3%	200 77.8%	302 94.4%	265 88.9%
IS AE	3218 83.8%	1825 74.4%	257 75.4%	180 68.4%	876 84.1%	513 70.9%	396 75.1%	176 68.5%	288 90.0%	238 79.9%
IS Pain	3157 82.2%	1763 71.9%	253 74.2%	175 64.3%	853 81.9%	489 66.0%	387 73.4%	175 68.1%	285 89.1%	235 78.9%
IS Swelling	941 24.5%	366 14.9%	81 23.8%	49 18.0%	259 24.9%	74 10.0%	122 23.1%	39 15.2%	66 20.6%	57 19.5%
IS Erythema	1005 26.2%	481 19.6%	59 17.3%	29 10.7%	207 19%	113 15.2%	97 18.4%	41 16.0%	64 20.0%	42 14.1%
Systemic	2275 59.3%	1503 61.3%	169 49.6%	127 48.3%	676 64.9%	468 64.6%	271 51.4%	120 46.7%	200 62.5%	196 65.8%
Pyrexia D1-15	386 10.1%	21.3 8.7%	39 11.4%	38 14.4%	181 17.4%	103 14.2%	107 20.3%	32 12.5%	69 21.6%	54 18.1%
Headache	975 25.4%	642 26.2%	74 21.7%	59 22.4%	371 35.6%	276 38.1%	82 15.6%	38 14.8%	100 31.3%	86 28.9%
Increased T D1-5	329/3821 8.6%	184/2446 7.5%	34/339 10%	37/261 14.1%	162/1036 15.6%	87720 12.1%	94/527 17.8%	24/257 9.3%	67/317 21.1%	52/297 17.5%
Subjects with SAEs	28 0.7%	19 0.8%	0 0.0%	2 0.8%	6 0.6%	1 0.1%	1 0.2%	2 0.8%	2 0.6%	2 0.7%

G=Gardasil; P=Placebo; IS = Injection Site; T = temperature
Source: From Appendices 2.7.4:98-117, Summary of clinical safety, p. 817-69

Adverse Events by HPV Status at Baseline: Safety was assessed in those who were PCR positive to at least 1 vaccine HPV type and seronegative to all 4 vaccine HPV types; seronegative to all 4 vaccine HPV types (regardless of PCR status); and those who were seropositive (regardless of PCR status).

TABLE 334
Protocols 005, 007, 013, 015, 016, 018: Summary of AEs by Baseline HPV Status

	PCR +, seronegative all 4 vacine HPV types		PCR neg., seronegative to all 4 vaccine HPV types		Seropositive to at least 1 vaccine HPV types, Regardless of PCR status		Seronegative to all 4 vaccine HPV types, Regardless of PCR status	
	G N=261	P N=233	G N=2889	P N=2541	G N=810	P N=682	G N=5323	P N=3365
Subjects with f/u	255	225	2852	2505	790	667	5252	3310
1+ AE	236 92.5%	199 88.5%	2640 92.6%	2247 89.7%	719 91.0%	565 84.7%	4717 89.8%	2845 86.0%
IS AE	217 85.1%	168 74.7%	2487 87.2%	1958 78.2%	666 84.3%	499 74.8%	4353 82.9%	2428 73.4%
IS Pain	211 82.7%	158 70.2%	2446 85.8%	1917 76.5%	657 83.2%	481 70.5%	4263 81.2%	2351 70.0%
IS Swelling	63 24.7%	40 17.8%	704 24.7%	395 15.8%	225 28.5%	99 14.5%	1242 23.6%	485 14.4%
IS Erythema	69 27.1%	45 20.0%	721 25.3%	484 19.3%	212 26.8%	94 13.8%	1217 23.2%	611 18.2%
Proportion with IS AE moderate to severe	91 35.7%	50 22.2%	925 32.4%	560 22.4%	278 35.2%	142 21.3%	1577 30%	658 19.8%
Frequency of IS AEs that were mild	521 75.8%	378 82.4%	6426 80.1%	4759 85.7%	1674 76.8%	1057 83.2%	10665 79.7%	5753 85.9%
Systemic	161 63.1%	144 64.0%	1863 65.3%	1614 64.4%	470 59.5%	383 57.4%	3111 59.2%	2027 61.2%
Pyrexia D1-15	35 13.7%	25 11.1%	358 12.6%	278 11.1%	136 17.2%	89 13.3%	645 12.3%	349 10.5%
Headache	73 28.6%	66 29.3%	871 30.5%	749 29.9%	228 28.9%	170 25.5%	1371 26.1%	929 28.1%
Proportion with systemic AE moderate or severe	103 40.4%	97 43.1%	1251 43.8%	1584 42.7%	341 43.1%	241 36.1%	1971 37.6%	1334 40.3%
Frequency with mild systemic AEs	258 52.7%	202 50.5%	2548 47.4%	2182 45.5%	661 45.0%	519 48.0%	4126 49.4%	2732 46.4%

TABLE 334 [Cont.] Protocols 005, 007, 013, 015, 016, 018: Summary of AEs by baseline HPV Status

	PCR +, seronegative all 4 vacine HPV types		PCR neg., seronegative to all 4 vaccine HPV types		Seropositive to at least 1 vaccine HPV types, Regardless of PCR status		Seronegative to all 4 vaccine HPV types, Regardless of PCR status	
	G N=261	P N=233	G N=2889	P N=2541	G N=810	P N=682	G N=5323	P N=3365
Increased T D1-5	32/251 12.7%	22/224 9.8%	314/2840 11.1%	246/2501 9.8%	125/786 15.9%	75/665 11.3%	561/5227 10.7%	308/3299 9.3%
Proportion of subjects with moderate or severe AE overall	143 56.1%	117 52.0%	1632 57.2%	1311 52.3%	440 55.7%	320 48.0%	2736 52.1%	1621 48.9%
Frequency of AEs that were mild overall	782 66.3%	583 67.6%	9024 67.0%	6956 67.1%	2341 64.0%	2361 67.0%	14856 68.0%	8506 67.4%
Subjects with SAEs	3 1.2%	5 2.2%	18 0.6%	15 0.6%	9 1.1%	5 0.7%	28 0.5%	21 0.6%

G=Gardasil; P=Placebo; IS = Injection Site; T = temperature
Source: From Tables 2.7.4:24, 25, 26, 27, p. 147-154; Appendices 2.7.4:118-153, p. 868-925

Safety of Higher Dose Formulations

In Protocol 007, higher dose formulations resulted in modest dose response for elevated Ts and injection site AEs. There was no apparent dose response for AEs in Protocol 016.

TABLE 335
Protocols 007 and 016: Clinical Adverse Experience Summary Day 1-15 after any Vaccination Visit in Subjects who Received Higher Dose Formulations and Partial Dose Formulations of Quadrivalent HPV 6, 11, 16, 18 Vaccine

Total VLP Dose	Aluminum Dose	N	Overall Adverse Experiences	Serious Adverse Experiences	Discontinuation Due to an Adverse Experience	Injection-Site Adverse Experiences	Severe Intensity Injection-Site Adverse Experiencess	Elevated Temp (>102°F)
Protocol 007								
Placebo	225 mcg	134	86.6%	0.0%	0.0%	74.6%	1.5%	0.0%
Placebo	450 mcg	140	90.0%	1.4%	0.7%	80.0%	2.1%	0.0%
120 mcg	225 mcg	272	91.9%	0.7%	0.0%	86.0%	2.9%	0.4%
160 mcg	225 mcg	269	93.3%	0.0%	0.7%	89.2%	5.9%	1.1%
280 mcg	395 mcg	277	95.7%	0.7%	0.0%	92.1%	5.1%	2.5%
Protocol 016								
24 mcg	225 mcg	496	89.5%	0.6%	0.4%	82.3%	Not summarized	1.8%
48 mcg	225 mcg	509	87.0%	0.0%	0.0%	79.8%	Not summarized	1.2%
72 mcg	225 mcg	507	88.2%	0.2%	0.2%	80.4%	Not summarized	1.2%
120 mcg	225 mcg	1015	91.3%	0.1%	0.1%	84.2%	Not summarized	1.5%

N = Number of subjects vaccinated.
HPV = Human papillomavirus; VLP = Virus-like particles.

Source: Appendix 2.7.4:154, p. 926

10.4.4 Product-Disease Interactions: Already discussed in integrated efficacy section 8.

10.4.5 Product-Product Interactions

Drug Interactions

Injection site AEs in those who took immunosuppressives

The proportions of subjects with an injection site AE appear similar to those in the overall Detailed Safety Population.

Systemic AEs in those who took immunosuppressives
The most common systemic AEs were headache (Gardasil 27.6%, placebo 34.5%), pyrexia (Gardasil 10.5%, placebo 11.0%), nausea (Gardasil 7.3%, placebo 8.2%), and nasopharyngitis/pharyngolaryngeal pain (Gardasil 7.1%, placebo 7.3 – 10.1%%). (Source: Appendix 2.7.4:157, p. 936-41, Summary of Clinical Safety, not shown here).

Injection site AEs in those who received Hepatitis B vaccine with Gardasil: In the groups who received Gardasil with or without Hepatitis B vaccine, there were higher proportions of subjects with an injection site AE in the 15 days after any vaccination visit (86.2, 83.6%) as compared to subjects who received the HPV placebo with or without hepatitis B vaccine (74.9, 75.4%).
There were higher proportions of subjects with injection site pain, swelling, and erythema in the groups that received the HPV vaccine with or without Hep B vaccine as compared to the groups that received HPV placebo with or without Hepatitis B vaccine. (Source: Appendix 2.7.4:172, p. 982-3, Summary of Clinical Safety, not shown here)

Systemic AEs in those who received Hepatitis B vaccine with Gardasil: The incidence rates of systemic AEs were similar for most events in the 4 treatment groups in Study 011. The group which received both active vaccines had the lowest proportion of subjects with systemic AEs (56.3%) as compared to the other groups (58.0-60.9%). However, there were a higher proportion of subjects who received HPV vaccine with or without Hepatitis B vaccine with pyrexia in the 15 days after any vaccination visit (20.7%, 22.2%) as compared to subjects who received HPV placebo with or without Hepatitis B vaccine (15.9%, 17.2%). One subject who received placebo in Study 011 had chondromalacia patellae diagnosed at Month 18. This condition occurs frequently in teenage girls when the articular cartilage softens in response to excessive and uneven pressure on the cartilage, thought to be related to overuse, trauma, and/or abnormal forces on the knee. Therefore, this condition does not appear related to an autoimmune process.[15]

[15] http://www.nlm.noh.gov/medlineplus/ency/article/000452.htm

TABLE 336
Protocol 011: Number (%) of Subjects with Systemic AEs (Incidence ≥ 1% in One or More Vaccination Group) by System Organ Class (Day 1 to 15 Following Any Vaccination Visit)

	G+ Hep B N=466	G + P N=468	GP+Hep B N=467	GP+P N=468
Subjects with follow-up	458	463	458	464
Subjects with one or more systemic AE	258 (56.3%)	282 (60.9%)	279 (60.9%)	269 (58.0%)
Headache	110 (24.0%)	126 (27.2%)	120 (26.3%)	126 (26.1%)
Pyrexia	95 (20.7%)	103 (22.2%)	73 (15.9%)	80 (17.2%)
Nausea	21 (4.6%)	30 (6.5%)	24 (5.2%)	25 (5.4%)
Diarrhea	15 (3.3%)	13 (2.8%)	9 (2.0%)	15 (3.2%)
Nasopharyngitis	22 (4.8%)	16 (3.5%)	22 (4.8%)	17 (3.7%)
Pharyngolaryngeal Pain	16 (3.5%)	12 (2.6%)	20 (4.4%)	14 (3.0%)
Dizziness	10 (2.2%)	11 (2.4%)	13 (2.8%)	14 (3.0%)
Skin Disorder	16 (3.5%)	22 (4.8%)	15 (3.3%)	10 (2.2%)
Abdominal Pain upper	7 (1.5%)	10 (2.2%)	8 (1.7%)	11 (2.4%)
Influenza	17 (3.7%)	17 (3.7%)	19 (4.1%)	16 (3.4%)
Dysmenorrhea	7 (1.5%)	10 (2.2%)	9 (2.0%)	10 (2.2%)
Abdominal Pain	17 (3.7%)	19 (4.1%)	9 (2.0%)	9 (1.9%)
Fatigue	5 (1.1%)	7 (1.5%)	10 (2.2%)	9 (1.9%)
Vomiting	8 (1.7%)	8 (1.7%)	6 (1.3%)	4 (0.9%)
Injury, poisoning and procedural complications	3 (0.7%)	5 (1.1%)	6 (1.3%)	7 (1.5%)
Myalgia	3 (0.7%)	9 (1.9%)	6 (1.3%)	7 (1.5%)
Cough	7 (1.5%)	6 (1.3%)	11 (2.4%)	3 (0.6%)
Back Pain	15 (2.8%)	10 (2.2%)	6 (1.3%)	10 (2.2%)
Malaise	6 (1.3%)	12 (2.6%)	6 (1.3%)	11 (2.4%)
Arthralgia	5 (1.1%)	4 (0.9%)	4 (0.9%)	3 (0.6%)
Ear and Labyrinth Disorders	5 (1.1%)	2 (0.4%)	8 (1.7%)	2 (0.4%)
Pharyngitis	5 (1.1%)	1 (0.2%)	9 (2.0%)	17 (3.7%)

GP=Gardasil Placebo
Source: Appendix 2.7.4:173, p. 984-9, Summary of Clinical Safety,

SAEs: There were few SAEs in any group: 0.2% (HPV placebo + Hep B vaccine), 0.4% (HPV vaccine + Hep B placebo), 0.7% (both active vaccines), and 1.1% (both placebos).
Source: Appendix 2.4.7:171, p. 980-1, Summary of Clinical Safety, not shown here

10.4.6 Immunogenicity

The Sponsor presented an integrated summary of immunogenicity across trials.
The **overall objective** was to summarize the overall immune responses to Gardasil across studies for various age subgroups at Month 7.

Additional objectives included (not all listed):

- Evaluate the impact of baseline covariates (age, gender and ethnicity) and deviations from vaccination regimen on anti-HPV responses at Month 7.
- Evaluate the impact of prior exposure to vaccine HPV types on vaccine induced immune responses at Month 7, along with the association between baseline vaccine type serostatus and Month 7 type specific immune responses.

- Provide summaries allowing bridging of the immunogenicity of 9-15 year old females from the Phase III immunogenicity studies to 16-26 year old female subjects from the Phase III efficacy studies.
- Evaluate the persistence of vaccine inducted anti-HPV responses for up to 1.5 years following the vaccination regimen, along with relationship between Month 7 and Month 24 responses.

Endpoints

The main immunogenicity endpoints included:

(1) anti-HPV 6, 11, 16, 18 serum cLIA GMTs at Months 0, 7, 12, 24

(2) anti-HPV 6, 11, 16, and 18 seroconversion (from seronegative to seropositive) rates. The seropositivity cutoffs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL and 24 mMU/mL, respectively.

Analysis Populations

Per-protocol immunogenicity population (PPI): This population included subjects who received all 3 vaccinations, had a Day 1 serum sample and Day 1 PCR sample (except for subjects 9-15 years of age in Protocols 016 and 018) within acceptable day range of the first vaccination, were seronegative before the first injection and were PCR negative through Month 7 for the relevant vaccine HPV type, did not receive non-study vaccines (inactivated 14 days before or after a dose of vaccine, or if for a live vaccine, within 21 days before or 14 Days after a dose of study vaccine), and did not receive immune globulin or blood products Day 1 through Month 7, did not receive immunosuppressives or have an immune disorder, was not enrolled in another study that might interfere with the results, had a month 7 visit within an acceptable day range, received all 3 doses within acceptable day range.

PPI for analyses of dosing deviations: This population was like the PPI population, but the allowable day ranges were wider in scope.

PPI regardless of steroid or immunosuppressive use from Day 1 through Month 7: This population was like the PPI but did not exclude subjects with steroid or immunosuppressive use.

Sponsor's Statitiscal Methods

GMTs and associated 95% CIs, and seroconversion rates and associated 95% CIs were primarily used in summaries for the various groups. Linear regression models were constructed to study the impact of baseline risk factors such as demographics, the natural log titer of the same HPV type at Day 1, the total number of other seropositive types at Day 1 and dosing deviation of vaccination regimen on the type specific Month 7 natural log titers.

Results (Females)

Overall Summaries of Month 7 Anti-HPV Serum cLIA Responses

The GMTs and seroconversion rates for each vaccine HPV type at Month 7 were generally similar across protocols. As was noted in the Phase III studies 015, 013, 007, 016, and 018, seroconversion indicated a change in serostatus from seronegative to seropositive. A subject was considered seronegative for HPV 6, 11, 16, and 18 if cLIA

titers were less than 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively. A subject was considered seropositive if the HPV 6, 11, 16, and 18 cLIA titers were $\geq$ 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL, respectively. As noted in Study 015, the cut-off for each HPV type was derived by repeatedly testing a panel of positive and negative samples against the standard curve. Among 18- to 26-year-old female recipients of Gardasil, the Month 7 anti-HPV 16 and anti-HPV 18 Geometric Mean Titers (GMTs) from Protocol 007 were higher compared with those from other protocols. The female adolescents (aged between 9 and 17) tended to have higher Month 7 GMTs for each vaccine HPV type than the female adults (aged between 18 and 26). The type-specific Month 7 GMTs of 16- to 17-year-old females were between those of female adolescents and adults.

TABLE 337
Protocols 007, 013, 015, 016: Month 7 HPV cLIA GMTs and Seroconversion Rates – 18 to 26 year old Females [PPI Population]

Assay (cLIA) Overall	Gardasil N=4666			
	N	GMT (95% CI)	M	Seroconversion rate (95% CI)
Anti-HPV 6	3133	544.6 (529.5, 560.2)	3128	99.8% (99.6, 99.9%)
Anti-HPV 11	3133	751.2 (727.4, 775.9)	3126	99.8% (99.5, 99.9%)
Anti-HPV 16	2992	2404.8 (2298.6, 2515.9)	2987	99.8% (99.6, 99.9%)
Anti-HPV 18	3361	473.7 (457.0, 491.1)	3344	99.5% (99.2, 99.7%)

Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:3, p. 17-18

TABLE 338
Protocols 007, 013, 015, 016: Month 7 HPV cLIA GMTs and Seroconversion Rates –9-17 year old Females [PPI Population]

Assay (cLIA) Overall	Gardasil			
	N	GMT (95% CI)	M	Seroconversion rate (95% CI)
Anti-HPV 6	1149	865.6 (820.6, 913.1)	1148	99.9% (99.5, 100%)
Anti-HPV 11	1149	1209.2 (1142.9, 1279.4)	1148	99.9% (99.5, 100%)
Anti-HPV 16	1144	4434.6 (4134.6, 4756.3)	1143	99.9% (99.5, 100%)
Anti-HPV 18	1170	912.1 (852.8, 975.5)	1166	99.7% (99.1, 99.9%)

Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:4, p. 19-20

TABLE 339
Protocols 007, 013, 015, 016: Month 7 HPV cLIA GMTs and Seroconversion Rates –16-17 year old Females [PPI Population]

Assay (cLIA) Overall	Gardasil			
	N	GMT (95% CI)	M	Seroconversion rate (95% CI)
Anti-HPV 6	222	637.7 (573.4, 709.1)	222	100% (98.4, 100%)
Anti-HPV 11	222	877.6 (778.4, 989.4)	222	100% (98.4, 100%)
Anti-HPV 16	215	2769.7 (2350.8, 3263.2)	215	100% (98.3, 100%)
Anti-HPV 18	238	533.4 (464.3, 612.7)	236	99.2% (97.0, 99.9%)

Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:5, p. 21-22

Analysis of Factors that Potentially Impact Month 7 Anti-HPV Responses
Immune responses were elicited by Gardasil in all ethnic and age groups and across all regions.

Ethnic groups
Hispanics had slightly higher Month 7 anti-HPV 6 GMTs as compared to the other ethnic groups. Hispanics, Caucasians, and blacks had slightly higher Month 7 anti-HPV 11 cLIA responses. Hispanics and blacks had slightly higher Month 7 anti-HPV 16 cLIA responses.
Asians had slightly higher Month 7 anti-HPV 18 cLIA responses.

Regions
North American subjects had slightly higher Month 7 GMTs than subjects in other regions.

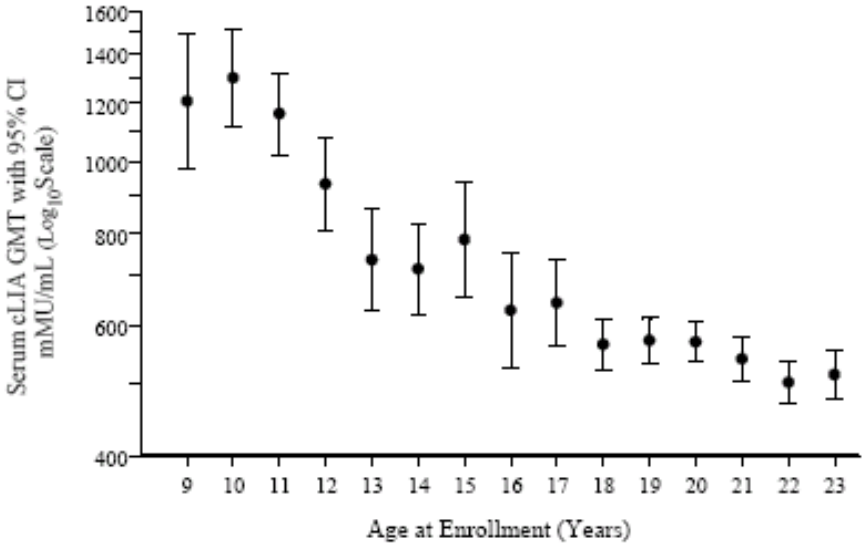
Age
For each vaccine HPV type, girls 9-15 years of age had higher Month 7 GMTs compared to women 18-26 years of age. For each vaccine HPV type, girls 16-17 years of age had slightly higher Month 7 GMTs compared to women 18-26 years of age.
In general, the type specific GMTs tended to decrease with an increase in the enrollment age. (See Table 340 below and Figures 33-36).

TABLE 340
Month 7 HPV cLIA GMTs by Baseline Subject Characteristics 9-26 year old Females who Received Gardasil (PPI Population)

	HPV 6		HPV 11		HPV 16		HPV 18	
Baseline Characteristics	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
Race								
Caucasian	2702	616.5 (596.5, 637.1)	2702	871.1 (839.7, 903.7)	2614	2702.7 (2571.3, 2840.9)	2860	536.6 (514.4, 559.7)
Black	184	597.5 (529.1, 674.4)	184	886.3 (780.0, 1007.1)	171	3498.8 (2926.7, 4182.7)	199	637.0 (548.8, 739.4)
Asian	319	576.9 (525.2, 633.7)	319	738.7 (665.1, 820.5)	314	2682.8 (2308.2, 3118.2)	327	662.9 (591.7, 742.8)
Hispanic	791	670.5 (630.8, 712.6)	791	889.7 (830.8, 952.8)	772	3528.4 (2984.7, 3557.1)	834	598.7 (553.8, 647.3)
Other	286	540.4 (497.1, 587.5)	286	720.3 (656.5, 790.4)	265	3036.2 (2683.9, 3434.7)	311	549.1 (491.7, 613.3)
Age (years)								
9-15	927	931.3 (876.9, 989.2)	927	1305.7 (1226.2, 1390.4)	929	4944.9 (4583.5, 5334.8)	932	1046.0 (971.2, 1126.5)
16-17	222	637.7 (573.4, 709.1)	222	877.6 (778.4, 989.4)	215	2769.7 (2350.8, 3263.2)	238	533.4 (464.3, 612.7)
18-26	3133	544.6 (529.5, 560.2)	3133	751.2 (727.4, 775.9)	2992	2404.8 (2298.6, 2515.9)	3361	474.7 (457.0, 491.1)
Region								
Asia/Pacific	431	583.7 (535.8, 635.8)	431	737.7 (671.4, 810.6)	417	2480.3 (2171.3, 2833.4)	439	589.4 (532.5, 652.5)
Europe	1242	598.4 (570.1, 628.2)	1242	850.0 (805.7, 896,7)	1194	2721.0 (2528.4, 2928.3)	1305	523.1 (491.7, 556.5)
Latin America	1466	576.9 (553.1, 601.7)	1466	794.2 (758.0, 832.1)	1411	2876.3 (2706.3, 3056.9)	1574	530.2 (502.7, 559.1)
North America	1143	708.8 (673.8, 745.6)	1143	993.7 (938.3, 1052.4)	1114	3111.7 (2876.1, 3366.5)	1213	639.5 (598.0, 683.9)

Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:7, p. 26

FIGURE 33
Protocols 007, 013, 015, 016, 018: Month 7 HPV 6 cLIA GMTs and 95% CIs at Enrollment: 9-16 year old Female Recipients of Gardasil (PPI)

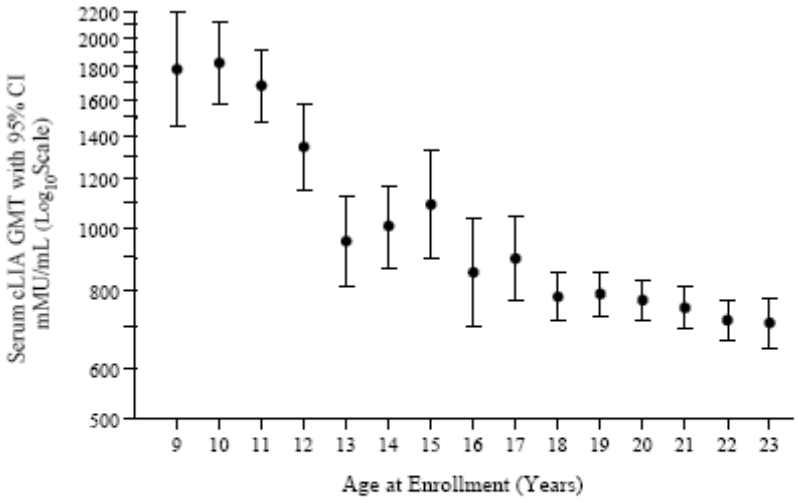


	Number of Subjects Evaluable (n)														
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	68	129	166	141	166	148	109	85	137	440	511	624	576	564	400

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:1, p. 27

FIGURE 34
Protocols 007, 013, 015, 016, 018: Month 7 HPV 11 cLIA GMTs and 95% CIs at Enrollment: 9-16 year old Female Recipients of Gardasil (PPI)

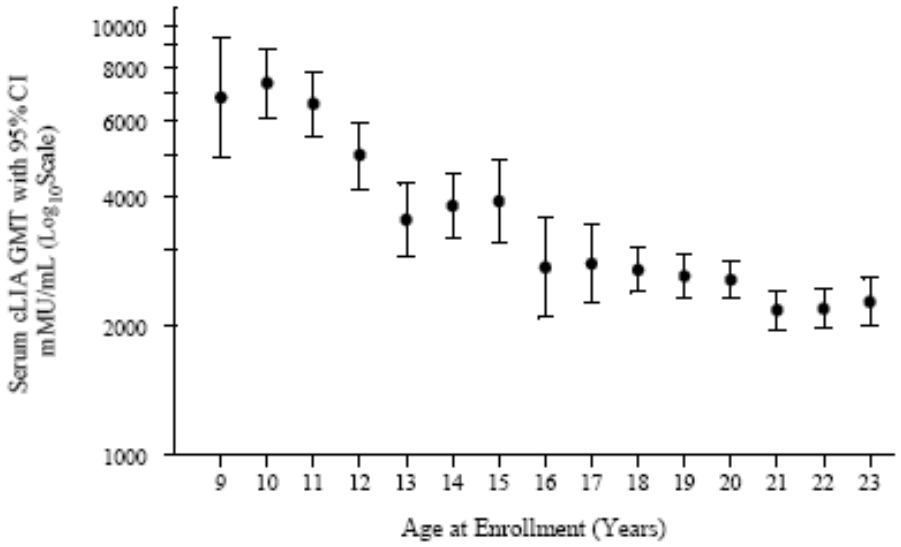


	Number of Subjects Evaluable (n)														
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	68	129	166	141	166	148	109	85	137	440	511	624	576	564	400

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:2, p. 28

FIGURE 35
Protocols 007, 013, 015, 016, 018: Month 7 HPV 16 cLIA GMTs and 95% CIs at Enrollment: 9-16 year old Female Recipients of Gardasil (PPI)

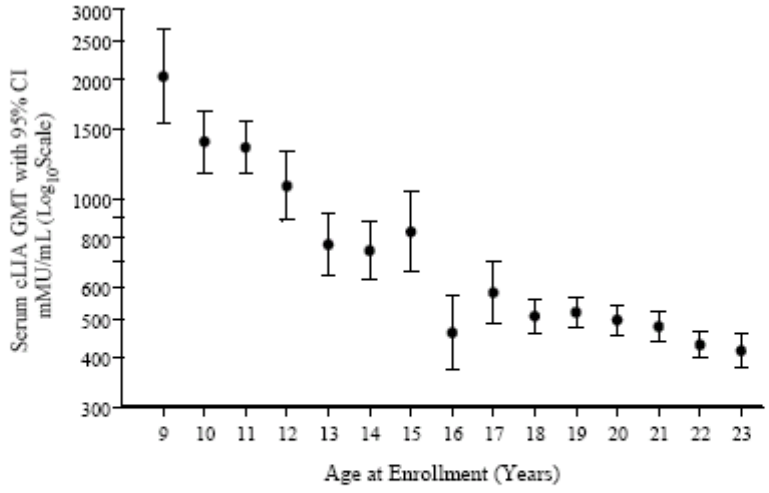


	Number of Subjects Evaluable (n)														
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	67	131	165	142	165	150	109	80	135	423	506	594	550	527	375

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:3, p. 29

FIGURE 36
Protocols 007, 013, 015, 016, 018: Month 7 HPV 18 cLIA GMTs and 95% CIs at Enrollment: 9-16 year old Female Recipients of Gardasil (PPI)



Number of Subjects Evaluable (n)															
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	68	130	166	142	167	150	109	88	150	463	554	649	619	620	439

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:4, p. 30

Regression models were used to assess whether baseline characteristics were predictors of immune response. The single factor approach modeled the type-specific Month 7 natural log titer as a function of the individual baseline predicting factor one at a time. The multiple factor approach modeled the type-specific Month 7 natural log titer as a function of several baseline predicting factors at the same time.

In the single factor models, the sponsor found that the following baseline characteristics were predictors of immune response:

- **Enrollment age** was a significant predictor of Month 7 anti-HPV 6, 11, 16, and 18 cLIA responses.
- **Race** was a significant predictor of Month 7 anti-HPV 11, 16, and 18 cLIA responses, with highest GMTs noted in Hispanic subjects, followed by Black, Caucasian, and Asian subjects.
- **Region** was a significant predictor of Month 7 anti-HPV 6, 11, and 16 cLIA responses, with highest GMTs noted in North America, followed by Europe, Latin America, and Asia.
- Baseline smoking, hormonal contraceptive use at Day 1, Pap test at or before Day 1 and lifetime number of male sexual partners were not significant predictors of any type Month 7 anti-HPV cLIA responses. (Source: Tables 5.3.5.3.3:8-11, p. 32-39, not shown here)

Impact of Day 1 HPV Serostatus and PCR status on Immunogenicity
For each vaccine HPV type, among the Gardasil recipients, subjects who were seropositive to the relevant vaccine HPV type at Day 1 had higher Month 7 GMTs than those who were seronegative at baseline.

TABLE 341
Month 7 cLIA GMTs by Day 1 Serostatus and PCR Status – 18 to 26 year old Females who Completed the Vaccination Regimen with Gardasil (N=4666) and Received Correct Clinical Material

HPV Type	Day 1 Serostatus	Day 1 PCR Status	N	GMT	95% CI
HPV 6	Negative	Negative	3582	552.2	537.7, 567.0
	Negative	Positive	89	590.6	492.1, 708.8
	Positive	Negative	244	1200.2	1045.1, 1378.3
	Positive	Positive	63	1260.2	978.7, 622.5
HPV 11	Negative	Negative	3582	758.9	736.2, 782.3
	Negative	Positive	17	1163.7	637.7, 2123.7
	Positive	Negative	66	1763.0	1324.5, 2346.7
	Positive	Positive	6	1754.8	N/A
HPV 16	Negative	Negative	3413	2428.4	2327.8, 2533.3
	Negative	Positive	188	2072.2	1717.5, 2500.2
	Positive	Negative	273	3437.0	2995.2, 3944.0
	Positive	Positive	165	2858.1	2341.2, 3489.1
HPV 18	Negative	Negative	3803	477.1	461.3, 493.5
	Negative	Positive	100	486.2	397.2, 595.0
	Positive	Negative	117	1110.4	930.2, 1325.5
	Positive	Positive	22	1012.5	582.4, 1760.3

Source: Integrated Summary of Immunogencity, Table 5.3.5.3.3:12, p. 41

Persistence of Anti-HPV 6, 11, 16, and 18 cLIA Responses
For each HPV type, in Gardasil recipients, the immune responses reached their highest level at Month 7, and then declined. In general, Gardasil recipients who were seropositive to the relevant vaccine HPV type at baseline had higher GMTs at Month 7, 12, and 24 compared to subjects who were seronegative at baseline.

TABLE 342
Protocols 007, 011, 012: HPV cLIA GMTs at Day 1, Month 7, Month 12, and Month 24 in 18-26 year old Female Subjects who Received Gardasil in the PPI population who had Serology Data at All Time Points

	Gardasil			
	N	GMT (95% CI)	M*	Seroconversion rate (95% CI)
Anti-HPV 6				
Month 7	1740	551.5 (531.0, 572.7)	1737	99.8% (99.5, 100%)
Month 12	1740	202.4 (194.1, 211.1)	1727	99.3% (98.7, 99.6%)
Month 24	1740	114.6 (109.5, 119.9)	1665	95.7% (94.6. 96.6%)
Anti-HPV 11				
Month 7	1740	770.4 (737.2, 805.2)	1736	99.8% (99.4, 99.9%)
Month 12	1740	252.8 (241.5, 264.6)	1726	99.2% (98.7, 99.6%)
Month 24	1740	144.9 (138.2, 151.8)	1698	97.6% (96.8, 98.3%)
Anti-HPV 16				
Month 7	1662	2407.1 (2262.9, 2560.4)	1660	99.9% (99.6, 100%)
Month 12	1662	957.4 (908.5, 1009.0)	1655	99.6% (99.1, 99.8%)
Month 24	1662	485.5 (461.4, 510.8)	1656	99.6% (99.2, 99.9%)
Anti-HPV 18				
Month 7	1869	499.2 (475.4, 524.2)	1862	99.6% (99.2, 99.8%)
Month 12	1869	119.7 (112.8, 127.0)	1678	89.8% (88.3, 91.1%)
Month 24	1869	56.2 (52.7, 60.0)	1381	73.9% (71.8, 75.9%)

*M-number who were seropositive
Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:14, p. 55

Several tables are provided that demonstrate higher anti-HPV levels for the relevant vaccine HPV type at Months 7, 12, and 24 in those who were seropositive and PCR negative, seropositive and PCR positive, and seronegative and PCR positive at baseline. **These tables also show that those who are seropositive at baseline have higher GMTs at Month 7, 12, and 24 as compared to those who are PCR positive at baseline but seronegative at baseline, as well as compared to those who are seronegative and PCR negative at baseline.** (Source: Integrated Summary of Immunoegenicity, Tables 5.3.5.3.3: 16, 17, 18, p. 58-60, not shown here)

The GMTs are also presented at these time points in females 16-17 years of age. The GMTs for this age group are slightly higher than those seen in the 18-26 year age group. Table 343 below shows the results for subjects 16-17 years of age.

TABLE 343
HPV cLIA GMTs at Day 1, Month 7, Month 12, and Month 24 in 16-17 year old Female Subjects who Received Gardasil in the PPI population who had Serology Data at All Time Points

	Gardasil			
	N	GMT (95% CI)	M*	Seroconversion rate (95% CI)
Anti-HPV 6				
Month 7	91	642.1 (539.8, 763.9)	91	100% (96.0, 100%)
Month 12	91	226.8 (188.1, 273.6)	90	98.9% (94.0, 100%)
Month 24	91	124.0 (100.9, 152.4)	86	94.5% (87.6, 98.2%)
Anti-HPV 11				
Month 7	91	966.7 (798.4, 1170.6)	91	100% (96.0, 100%)
Month 12	91	302.8 (250.3, 366.3)	91	100% (96.0, 100%)
Month 24	91	160.8 (129.7, 199.3)	89	97.8% (92.3, 99.7%)
Anti-HPV 16				
Month 7	94	2580 (2003.7, 3321.9)	94	100% (96.2, 100%)
Month 12	94	963.7 (768.8, 1207.9)	94	100% (96.2, 100%)
Month 24	94	469.3 (361.0, 610.2)	92	97.9% (92.5, 99.7%)
Anti-HPV 18				
Month 7	103	502.1 (408.8, 616.8)	103	99.0% (94.7, 100%)
Month 12	103	120.3 (96.2, 150.4)	103	92.2% (85.3, 96.6%)
Month 24	103	54.5 (42.2, 70.5)	103	72.8% (63.2, 81.1%)

Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.

*M-number who were seropositive

Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:18, p. 60

Table 344 below presents the immune responses in females 18-26 years of age with data available at the corresponding time point.

TABLE 344
HPV cLIA GMTs at Day 1, Month 7, Month 12, and Month 24 in 18-26 year old Female Subjects who Received Gardasil in the PPI Population who had Serology Data at the Corresponding Time Point

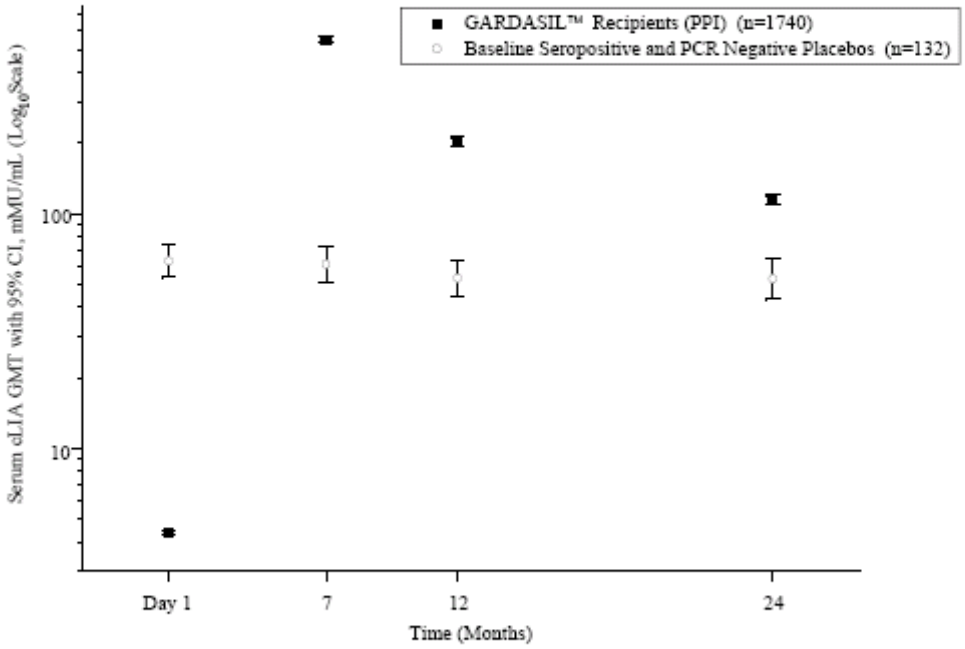
	Gardasil			
	N	GMT (95% CI)	M*	Seroconversion rate (95% CI)
Anti-HPV 6				
Month 7	2861	539.8 (524.3, 555.8)	2856	99.8% (99.6, 99.9%)
Month 24	2673	111.7 (107.7, 115.9)	2556	95.6% (94.8, 96.4%)
Anti-HPV 11				
Month 7	2861	752.6 (727.7, 778.4)	2854	99.8% (99.5, 99.9%)
Month 24	2673	141.2 (135.9, 146.6)	2607	97.5% (96.9, 98.1%)
Anti-HPV 16				
Month 7	2734	2376.9 (2267, 2492.1)	2729	99.8% (99.6, 99.9%)
Month 24	2569	464.4 (445.8, 483.8)	2556	99.5% (99.1, 99.7%)
Anti-HPV 18				
Month 7	3070	475.0 (457.5, 493.2)	3056	99.5% (99.2, 99.8%)
Month 24	2866	52.2 (49.5, 55.0)	2050	71.5% (69.8, 73.2%)

Seroconversion = change in serostatus from seronegative to seropositive. The seropositvity cut-offs for HPV 6, 11, 16, and 18 were 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL.
*M=Number of subjects who seroconverted
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3: 19, p. 61

Figures 37-40 show the anti-HPV 6, 11, 16, and 18 GMTs at Month 24 in Gardasil recipients compared to those who were seropositive at baseline and received placebo. In general, the GMTs are highest at Month 7, and appear to remain higher compared to those who were seropositive at baseline but received placebo.

FIGURE 37

Persistence of Anti-HPV 6 cLIA Responses in 18- to 26-Year-Old Female Recipient—GARDASIL™ Recipients Seronegative at Day 1 and PCR Negative Through Month 7 (PPI) Versus Placebo Recipients Seropositive and PCR Negative at Day 1
(Cohorts With Serology Data at All Time Points)

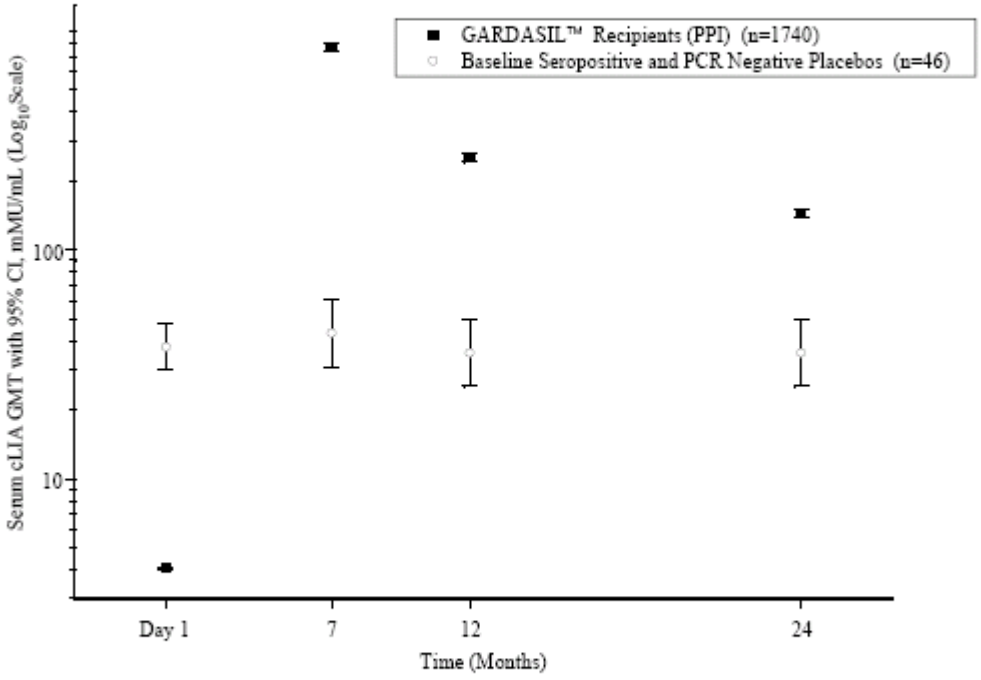


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figures 5.3.5.3.3: 13, p. 66

FIGURE 38

Persistence of Anti-HPV 11 cLIA Responses in 18- to 26-Year-Old Female Recipient—GARDASIL™ Recipients Seronegative at Day 1 and PCR Negative Through Month 7 (PPI) Versus Placebo Recipients Seropositive and PCR Negative at Day 1
(Cohorts With Serology Data at All Time Points)

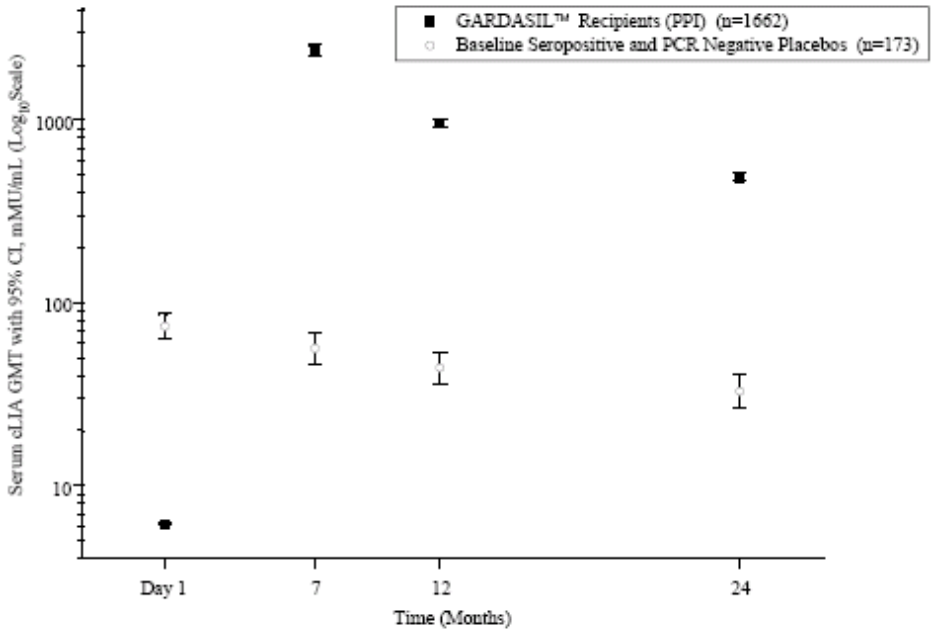


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Intgrated Summary of Immunogenicity, Figures 5.3.5.3.3: 14, p. 67

FIGURE 39

Persistence of Anti-HPV 16 cLIA Responses in 18- to 26-Year-Old Female Recipient—GARDASIL™ Recipients Seronegative at Day 1 and PCR Negative Through Month 7 (PPI) Versus Placebo Recipients Seropositive and PCR Negative at Day 1 (Cohorts With Serology Data at All Time Points)

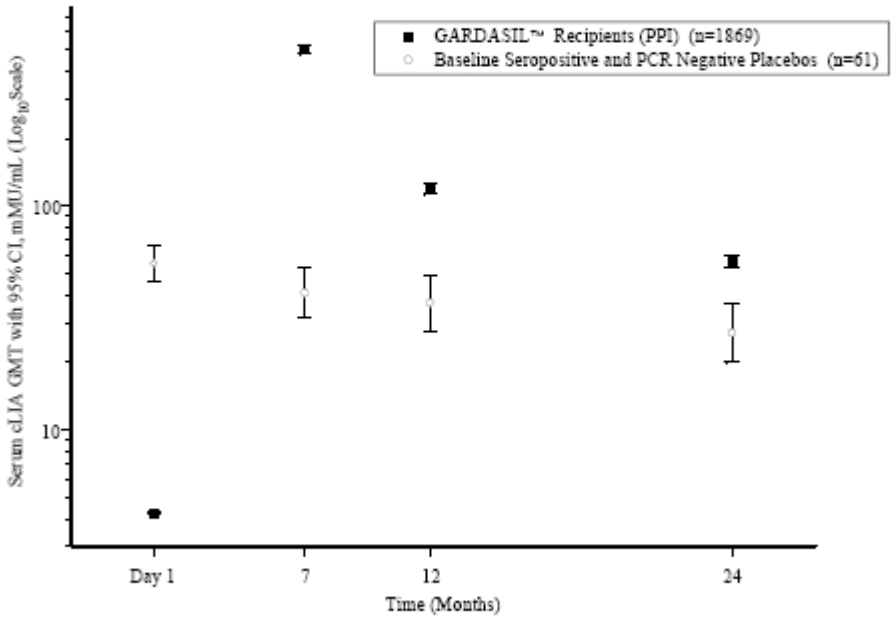


HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Intgrated Summary of Immunogenicity, Figure 5.3.5.3.3:15, p. 68

FIGURE 40

Persistence of Anti-HPV 18 cLIA Responses in 18- to 26-Year-Old Female Recipient—GARDASIL™ Recipients Seronegative at Day 1 and PCR Negative Through Month 7 (PPI) Versus Placebo Recipients Seropositive and PCR Negative at Day 1
(Cohorts With Serology Data at All Time Points)



HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:16, p. 69

Impact of Dosing Deviations on Immunogenicity

The sponsor also conducted an exploratory analysis to evaluate the effect of variation of dosing schedule on resulting GMTs at Month 7 (timing of dose 2 in Table 345 and timing of dose 3 in Table 346). An immune response was documented with early and late variation of administration of dose 2, although there was a somewhat higher response in GMTs when dose 2 was administered earlier than the planned administration at Month 2. There was a higher GMT when dose 3 was administered somewhat later than the scheduled dose at Month 6. The significance of these differences is not clear.

TABLE 345
Impact of Time Between Vaccinations 1 and 2 on Month 7 cLIA GMTs – 18 to 26 year old Female Recipients of Gardasil (PPI Approach for Analysis of Dosing Deviation)

Assay	Interval between Vaccinations 1 & 2	N	GMT (95% CI)	Model Based GMT*
Anti-HPV 6	Early (36-50 days)	939	578.1 (549.4, 608.2)	592.2
	On Time (51-70 days)	1884	548.1 (528.9, 568.0)	546.8
	Late (71-84 days)	323	446.7 (405.5, 492.0)	509.9
Anti-HPV 11	Early (36-50 days)	939	836.4 (788.8, 886.9)	842.0
	On Time (51-70 days)	1884	742.1 (712.3, 773.1)	757.0
	Late (71-84 days)	323	610.4 (548.5, 679.1)	689.7
Anti-HPV 16	Early (36-50 days)	898	2665.1 (2455.8, 2892.4)	2694.8
	On Time (51-70 days)	1811	2390.4 (2256.8, 2531.9)	2363.1
	Late (71-84 days)	294	1886.5 (1625.1, 2189.0)	2106.6
Anti-HPV 18	Early (36-50 days)	997	522.0 (487.7, 558.0)	534.9
	On Time (51-70 days)	2037	466.8 (446.0, 488.7)	475.9
	Late (71-84 days)	347	388.6 (349.5, 432.1)	429.6

The model based GMT was calculated given that age=21, interval between vaccinations 2 and 3=122 days, interval between Month 7 serum sample and vaccination 3=30 days, while the interval between vaccinations 1 and 2 is 45, 61, 75 days for "Early", "On Time" or "Late" analysis, respectively.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:24, p. 76

TABLE 346
Impact of Time Between Vaccinations 2 and 3 on Month 7 cLIA GMTs – 18 to 26 year old female recipients of Gardasil (PPI Approach for analysis of dosing deviation)

Assay	Interval between Vaccinations 2 & 3	N	GMT (95% CI)	Model Based GMT*
Anti-HPV 6	Early (80-105 days)	521	491.1 (459.8, 524.7)	506.0
	On Time (days)	2221	548.6 (530.6, 567.1)	546.8
	Late (71-84 days)	349	592.7 (541.6, 648.5)	590.9
	Very Late (161-200 days)	55	680.6 (546.8, 847.0)	638.6
Anti-HPV 11	Early (36-50 days)	521	663.6 (614.2, 716.9)	679.4
	On Time (51-70 days)	2221	755.1 (726.9, 784.5)	757.0
	Late (71-84 days)	349	877.8 (794.2, 970.3)	843.5
	Very Late (161-200 days)	55	891.6 (682.3, 1165.1)	939.8
Anti-HPV 16	Early (36-50 days)	501	2171.6 (1949.6, 2419.0)	2236.8
	On Time (51-70 days)	2113	2416.9 (2290.6, 2550.2)	2363.1
	Late (71-84 days)	337	2764.0 (2411.8, 3167.6)	2496.7
	Very Late (161-200 days)	52	2580.5 (1795.2, 3709.4)	2637.8
Anti-HPV 18	Early (36-50 days)	552	416.6 (383.6, 452.4)	454.3
	On Time (51-70 days)	2386	482.1 (461.8, 503.3)	475.9
	Late (71-84 days)	379	502.5 (450.0, 561.2)	498.6
	Very Late (161-200 days)	64	511.5 (382.6, 683.8)	522.3

* The model based GMT was calculated given that age=21, interval between vaccinations 1 and 2=61 days, interval between Month 7 bleed and vaccination 3=30 days, while the interval between vaccinations 2 and 3 is 92, 122, 152 or 182 days for "Early", "On Time", "Late" or "Very Late" analysis, respectively.
Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:25, p. 77

Impact of Hormonal Contraception on Immunogenicity

There was no apparent impact of use of hormonal contraceptives on Month 7 anti-HPV GMTs for all vaccine HPV types.

TABLE 347
Summary of Month 7 HPV cLIA GMTs – 18-26 year old Female Recipients of Gardasil by Status of Hormonal Contrcaeptive Use From Day 1 through Month 7 (PPI population)

	Subjects with Hormonal Contraceptive Use From Day 1 through Month 7 (N=3525)		Subjects without Hormonal Contraceptive Use through Month 7 (N=1137)	
Assay	N	GMT (95% CI)	N	GMT (95% CI)
Anti-HPV 6	2409	543.3 (526.6, 560.6)	724	549.0 (515.4, 584.9)
Anti-HPV 11	2409	753.1 (726.5, 780.7)	724	745.0 (693.1, 800.9)
Anti-HPV 16	2292	2378.6 (2259.3, 2505.3)	700	2492.4 (2268.2, 2738.7)
Anti-HPV 18	2590	474.4 (455.5, 494.1)	771	471.3 (436.3, 509.2)

Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:26, p. 82

Immunogenicity Bridging

9-15 year old female subjects in Protocols 016 and 018 had higher GMTs than 16-26 year old subjects in the efficacy studies (Protocols 013 and 015) for each vaccine HPV type. RCDF curves are also provided for each HPV type. The results of statistical comparisons between 16-23 year old females and 10-15 year old females were presented in Protocol 016. Table 348 shows the observational difference between GMTs in 9-15 year old females participating in studies 016 and 018 as compared to 16-26 year old subjects who participated in the efficacy studies. In addition, Reverse Cumulative Distribution Function plots are provided for these populations in Figures 41-44.

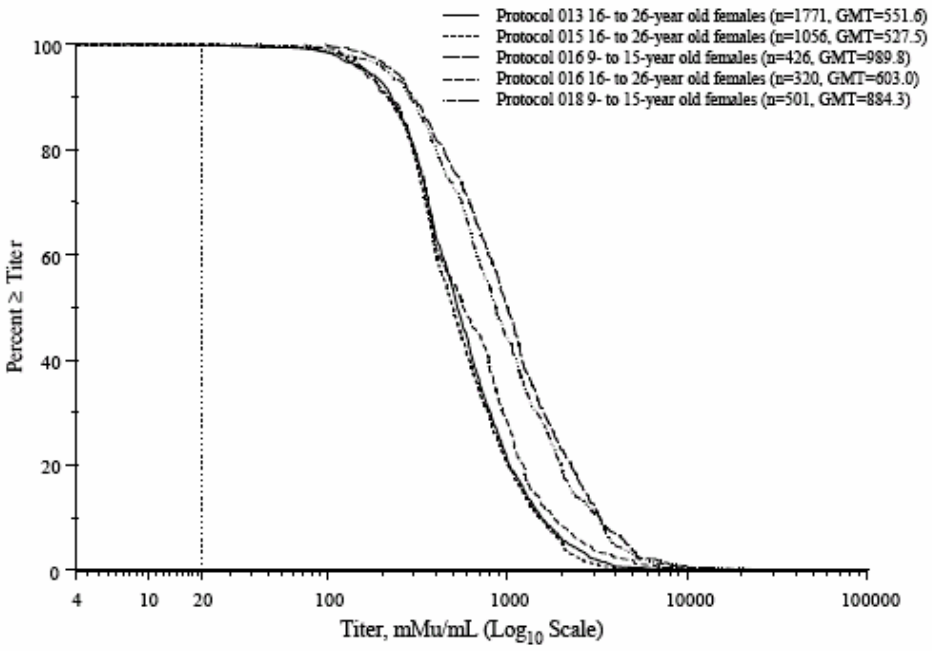
TABLE 348
Immunogenicity Bridging Between 9-15 year old Females in the Immunogenicity studies in 16-26 year old Female Recipients of Gardasil in Efficacy Studies (PPI population)

	9-15 year old females subjects (Studies – Protocols 016 and 018) N-1121		16-26 year old female subjects (Efficacy Studies –Protocols 013 and 015) N=4229	
Assay	N	GMT (95% CI)	N	GMT (95% CI)
Anti-HPV 6	927	931.3 (876.9, 989.2)	2827	542.4 (526.6, 558.7)
Anti-HPV 11	927	1305.7 (1226.2, 1390.4)	2827	766.1 (740.5, 792.6)
Anti-HPV 16	929	4944.9 (4583.5, 5334.8)	2707	2313.8 (2206.2, 2426.7)
Anti-HPV 18	932	1046.0 (971.2, 1126.5)	3040	460.7 (443.8, 478.3)

Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:29, p. 85

FIGURE 41

Reverse Cumulative Distribution Function Plot of the Month 7 Anti-HPV 6 cLIA Responses—Immunogenicity Bridging Between Phase III Protocols (Per-Protocol Immunogenicity Population)

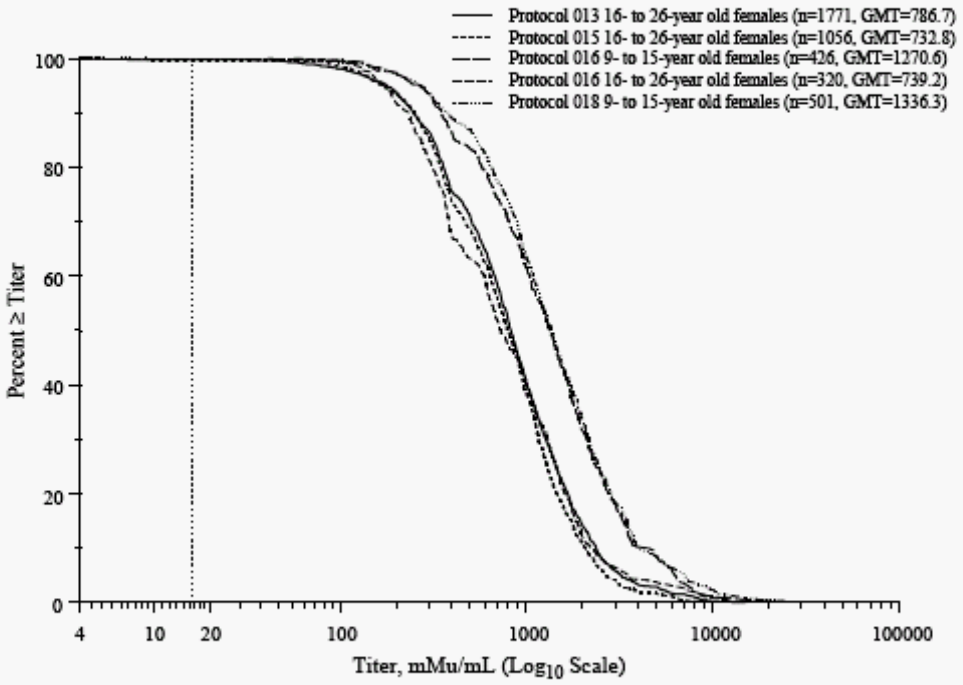


Note: The vertical line corresponds to the anti-HPV 6 cLIA cutoff value for being seropositive to HPV 6.
HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Table 5.3.5.3.3:25, p. 86

FIGURE 42

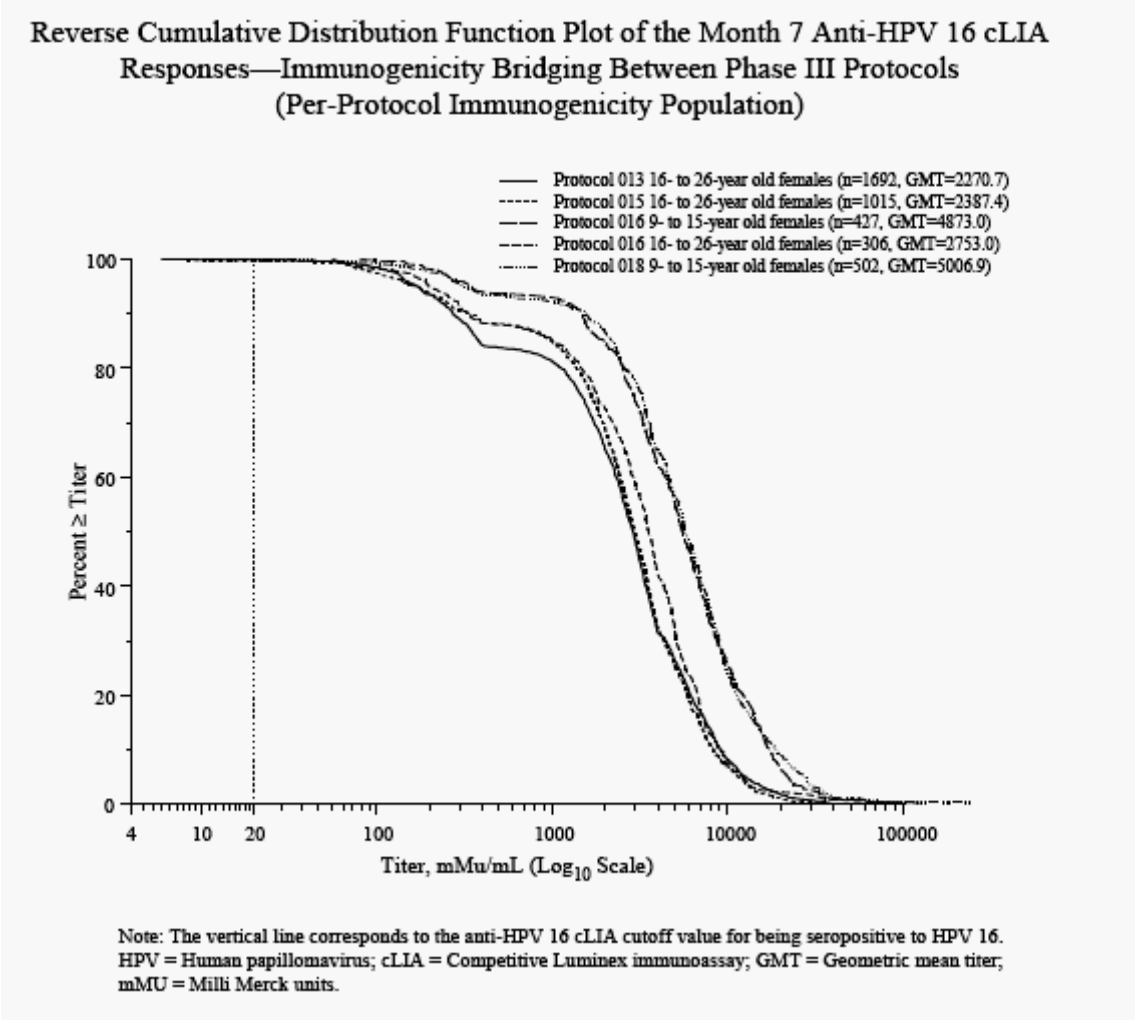
Reverse Cumulative Distribution Function Plot of the Month 7 Anti-HPV 11 cLIA Responses—Immunogenicity Bridging Between Phase III Protocols (Per-Protocol Immunogenicity Population)



Note: The vertical line corresponds to the anti-HPV 11 cLIA cutoff value for being seropositive to HPV 11.
HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3:25, p. 87

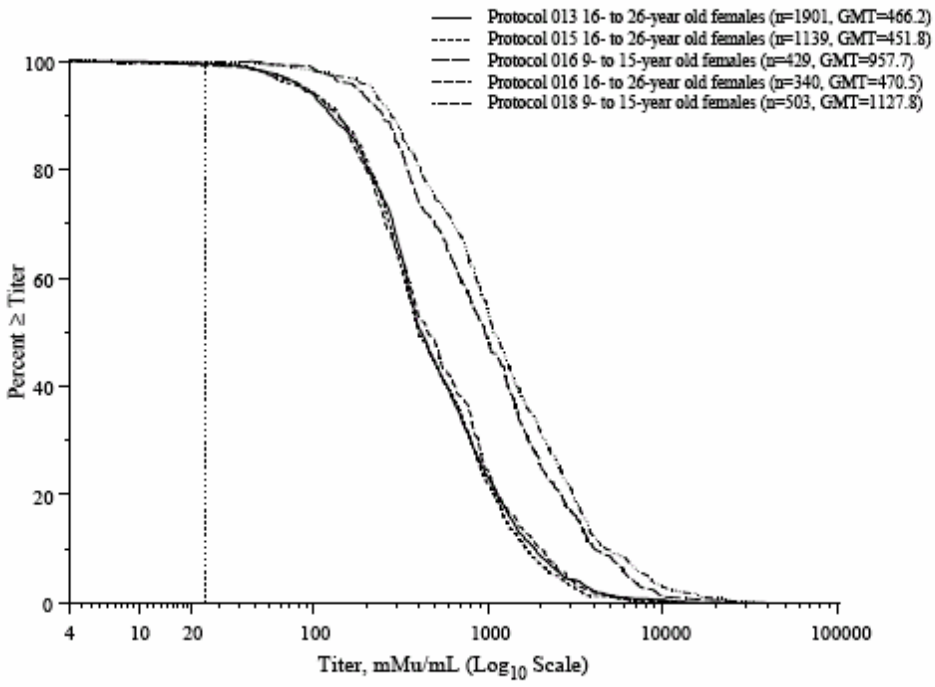
FIGURE 43



Source: Integrated Summary of Immunogenicity Figure 5.3.5.3.3:27, p.88

FIGURE 44

Reverse Cumulative Distribution Function Plot of the Month 7 Anti-HPV 18 cLIA Responses—Immunogenicity Bridging Between Phase III Protocols (Per-Protocol Immunogenicity Population)



Note: The vertical line corresponds to the anti-HPV 18 cLIA cutoff value for being seropositive to HPV 18.
HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Source: Integrated Summary of Immunogenicity, Figure 5.3.5.3.3: 28, p. 89

10.4.7 Human Carcinogenicity: No testing conducted.

10.4.8 Withdrawal Phenomena/Abuse Potential: Not applicable

10.4.9 Human Reproduction and Pregnancy Data:
Please see discussions under Safety regarding pregnancy data. Also, preclinical toxicology studies and reproductive toxicology studies were conducted with Gardasil. These studies were reviewed in detail by Dr. Sally Hargus and Dr. Marion Gruber, respectively. Please see their reviews for full assessment.

10.4.10 Assessment of Effect on Growth: No testing was conducted.

10.4.11 Overdose Experience: When subjects were inadvertently given 0.75 mL Gardasil, most of the AEs were injection site AEs (mild to moderate), and of short duration. Systemic AEs were also mild to moderate and of short duration. Subjects who received Hepatitis B vaccine overdose experienced predominantly local injection site reactions (mild to moderate in severity). (Source: Appendix 2.7.4: 197, p. 1093-5, not shown here)

10.4.12Person-to-Person Transmission, Shedding: This product is not a live viral product, so there is no issue of vaccine shedding or person-to-person transmission.

10.4.13 Post-Marketing Experience: None to date, original BLA review.

10.5 Safety Conclusions

In females 9-26 years of age, Gardasil, when administered in a 3 dose regimen at 0, 2, and 6 months appeared to produce comparable adverse event profiles in those who received placebo (alum and and saline) with a few exceptions.

There was a somewhat higher proportion of Gardasil recipients as compared to placebo recipients with an injection site adverse event in the 5 days after any vaccination, and there was a somewhat higher proportion of Gardasil recipients with a complaint that was moderate or severe as compared to placebo recipients. Pain, swelling, and erythema were the most common injection site adverse events.

There was a comparable proportion of subjects in each group with a systemic adverse event in the 15 days after any vaccination. The most common systemic adverse events included headache, pyrexia, and nausea.

There were comparable rates of deaths and SAEs in both treatment groups.

There were very few discontinuations in either group due to an adverse event.

New medical conditions in the vaccination period and post-month 7 period were generally balanced between the treatment groups.

There were a small number of subjects who developed a new autoimmune disorder in the vaccine and placebo group. A majority of the subjects who developed such illnesses had pre-vaccination symptoms of joint pain, and incidence of rates of specific autoimmune diseases noted in these studies were, in general, not higher than the incidence rates reported in the literature. However, there were a few subjects without previous symptoms. Collection of autoimmune adverse events will occur for a 6 month time period in the short term adverse event study to be conducted in 44,000 subjects in a large managed care organization as a post-marketing cmmittment.

The SAEs that occurred in women who became pregnant were comparable in the vaccine and placebo groups.

There was a similar number of infants with a congenital anomaly born to mothers who received Gardasil or placebo. However, there was an imbalance in the number of infants with a congenital anomaly born to mothers who were vaccinated within 30 days of vaccination with Gardasil (5) as compared to those who received placebo (0). No discernible pattern was identified. A pregnancy registry will be included as a post-marketing commitment as discussed earlier. The vaccine will be classified as Category B, but administration of vaccine is not recommended in a patient known to be pregnanct.

There were a slightly higher number of infants who developed a respiratory infection if their mothers received Gardasil while breastfeeding (3.4%) as compared to those who received placebo (1.9%). Of note, the mothers of these infants received other doses of Gardsil without a respiratory event occurring in these infants, and the dose after such an event occurred was ariable. In infants of subjects

who were not breastfeeding, it was noted that there was a similar number of infants with potentially exposed to study material in the placebo group with a respiratory event (13 [including 5 neonatal respiratory distress syndrome events]) as compared to the Gardasil group (14 [including 2 neonatal respiratory distress syndrome, one of which occurred in a child with a congenital anomaly]). When the infants who were breastfeeding and developed a respiratory event were included, there were 26 infants in the Gardasil group and 19 in the placebo group. The numbers were small, and the intervals between vaccination and the events were variable, so a definitive association was not apparent. However, caution is noted in the label if the mother is breastfeeding and receives the vaccine.

In infants born to mothers who received Gardasil as compared to placebo at sometime during gestation, there was a slightly higher number of subjects in the Gardasil group (app. 5.8% of live births) who experienced an SAE as compared to those whose received placebo. The types of events that occurred were comparable in both groups, and there were long intervals between the potential exposure and the event. Thus, at this time, there is no clear relationship of the event to vaccination with Gardasil. Pregnancy outcomes in additional subjects who became pregnant will be included in the close-outs of studies 013 and 015, and a pregnancy registry is also planned. (See post-marketing commitments in approval letter).

11. **Additional Clinical Issues:**

The clinical issues of concern (including efficacy in the seropositive and PCR positive subjects, possible replacement of vaccine HPV types with non-vaccine HPV types, question of relationship of vaccine administration to congenital anomalies, possible increase in respiratory events in infants whose mothers were breastfeeding during the vaccination period, and duration of immune responses) have been discussed within the sections of overall efficacy, safety, and immunogenicity.

Efficacy trials are ongoing in males 16-23 years of age and in women older than 26 years of age. Results are awaited.

11.1 **Directions for Use**

Gardasil is supplied as a single dose vial or as a prefilled syringe. The vaccine should be used as supplied. No dilution or reconstitution is necessary. The vaccine should be thoroughly agitated prior to administration.

11.2 **Dose Regimens and Administration:** Gardasil should be administered intramuscularly as 3 separate 0.5 mL doses according to the following schedule:
First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose
The same dose is administered to ages 9-26 year old females.
Gardasil should be administered intramuscularly in the deltoid region of the upper arm or in the anterolateral area of the thigh.

11.3 **Special Populations:** The product has not been tested in subjects with severe immunosuppresssion or HIV infection.

11.4 **Pediatrics:** CBER is allowing the sponsor to defer pediatric studies for Gardasil in girls less than 9 years of age and in boys and adolescent males less than 18 years of age.

12. **Conclusions – Overall**

Available data appear adequate to support the safety and efficacy of Gardasil in females 9-26 years of age who are naïve to the specific vaccine HPV type. The conclusion regarding efficacy in prevention of vaccine related CIN, AIS, and external genital lesions in females 16-23 years of age is based on 4 efficacy trials which utilized histopathololgical endpoints which included identification of the vaccine HPV type within the same specimen. Efficacy was inferred in the 9-15 year old female group because of immune responses that were non-inferior to those seen in the 16-23 year old female population. Females who are naïve to vaccine HPV types are expected to derive the most benefit from the vaccine in prevention of vaccine related HPV disease. Other females who are PCR positive and/or seropositive for one or more of vaccine HPV types may still benefit in prevention of disease due to HPV type(s) for which they are not already PCR positive and/or seropositive.

Safety issues have been discussed in the Safety conclusions above, and other clinical issues also discussed within the overall sections on efficacy and immunogenicity.

13. **Recommendations**

13.1 **Approval Recommendations**

The clinical data provided support approval of Gardasil in females 9-26 years of age.

13.2 **Recommendations on Postmarketing Actions**

The sponsor has agreed to conduct several post-marketing commitments. These are discussed in the Executive Summary and are described in the approval letter as noted below.

- The sponsor has committed to conduct a short-term safety surveillance study in a U.S. Managed Care Organization (MCO). The study will include approximately 44,000 vaccinated subjects who will be followed for 60 days for assessment of general short-term safety (i.e., emergency room visits, hospitalizations, and deaths). The subjects will also be followed for 6 months subsequent to vaccination for new autoimmune disorders, rheumatologic conditions, or thyroiditis. Also, a sufficient number of children 11-12 years of age will be studied to permit an analysis of safety outcomes. The final study protocol will be submitted by December 31, 2006. Patient accrual will be completed by December 31, 2008. The study will be completed by June 30, 2009. The final study report will be submitted by September 30, 2009.
- The sponsor has committed to collaborate with the cancer registries in four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASIL. In this study, approximately 5,500 subjects enrolled in Protocol 015 (one half from the placebo group that will have been vaccinated shortly after approval) will be followed for a total of 14 years. Two major goals of this study are: 1) to assess the long-term effectiveness of GARDASIL by

evaluating biopsy specimens for presence of HPV 6/11/16/18-related incident breakthrough cases of CIN 2/3, AIS and cervical cancer, VIN 2/3 and vulvar cancer, and VaIN 2/3 and vaginal cancer; and 2) to assess whether administration of GARDASIL will result in replacement of these diseases due to vaccine HPV types with diseases due to non-vaccine HPV types. The final protocol for this study will be submitted by December 8, 2006. Patient accrual for this study was previously completed in the context of Protocol 015. This study will be completed by December 31, 2017, (14 years from initiation of the last patient enrolled in Protocol 015 in the four Nordic countries). The final study report will be submitted by December 31, 2018.

- The sponsor has committed to conduct a study in collaboration with the Norwegian Government, if GARDASIL is approved in the European Union and the Government of Norway incorporates HPV vaccination into its national guidelines, to assess the impact of HPV vaccination on the following in Norway:
  a. The long-term burden of HPV disease including the incidence of HPV 6/11/16/18-related cervical disease;
  b. The long-term burden of HPV disease caused by types other than HPV 6/11/16/18;
  c. The overall incidence of cervical HPV disease;
  d. The incidence of HPV-related cancers and pre-cancers (CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer);
  e. The interaction between administration of GARDASIL and pregnancy outcomes, especially congenital anomalies, by linking the vaccination registry with the Medical Birth Registry.
- The sponsor has committed to submit final Clinical Study Reports (CSRs) for Protocols 013 and 015 when completed. As discussed, for these studies, an "all CIN 2/3, AIS or cervical cancer" analysis will evaluate the evidence for replacement of disease due to HPV types 16 and 18 with non-vaccine HPV types. Similar analyses will be done for VIN 2/3, VaIN 2/3, vulvar cancer and vaginal cancer. Protocol 013 was submitted in December 2001, and Protocol 015 was submitted in May 2002. Protocol 013 accrual was completed in March 2003, and Protocol 015 accrual was completed in May 2003. These analyses will be completed by April 30, 2007. The final reports for these studies (i.e., CSRs) to include the results of these analyses will be submitted by June 30, 2007.
- The sponsor has committed to provide data concerning duration of immunity following administration of GARDASIL® as follows from the studies noted:
  a. The Nordic Long-Term Follow-up Study: Interim reports of effectiveness (i.e., incident breakthrough cases of CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer) and immunogenicity results will be submitted in 2009, 2011, 2013, and 2015. The final study report will be submitted by December 31, 2018.
  b. Protocol 018 (Adolescent Sentinel Cohort): Periodic reports beginning with Month 24 immunogenicity and long-term safety data will be submitted starting no later than March 30, 2007; publication of one year Post-dose 3 data will be submitted by January 30, 2007; a Biologics License Supplement (BLS) for 1.5 year Post-dose 3 data will be submitted by June 30, 2007; a Biologics License Supplement (BLS) for 2.5 year Post-dose 3 data will be submitted by December 31, 2007; a Biologics

License Supplement (BLS) for 5.5 year Post-dose 3 data will be submitted by December 31, 2010.

c. Protocol 007: Publication of five-year immunogenicity data will be submitted by December 31, 2006.
d. Protocol 005: Publication of seven and one half year immunogenicity data will be submitted by December 31, 2007.

- The sponsor has agreed to establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL during pregnancy. The sponsor has committed to submit a protocol for the U.S. pregnancy registry by July 20, 2006 and agreed to address elements found in FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries (9/2/2002) (http://www.fda.gov/cber/gdlns/pregexp.htm), as well as relevant Company Standard Operating Procedures. Patient accrual/data collection will begin at time of CBER's approval of the protocol and end five years later. The sponsor will submit annual reports and a final summary report of the U.S. pregnancy registry's findings five years after initiation of patient accrual/data collection. The U.S. pregnancy database will be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report will be submitted to CBER five years and six months after initiation of patient accrual/data collection. After reviewing the five-year data, Merck and CBER will meet to discuss the need to continue further data collection in the U.S. pregnancy registry. CBER will have final approval regarding any decision to discontinue the U.S. pregnancy registry.
- **Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:** The sponsor has committed to provide CBER and simultaneously the FDA contractor for the Vaccine Adverse Events Reporting System (VAERS) all initial postmarketing "periodic" adverse experience reports received that are subject to periodic reporting (i.e., not covered under the "15-day Alert report" requirement under 21 CFR 600.80) on a monthly basis. Initial reports received by Merck in a given month will be submitted on VAERS forms to CBER and to the VAERS contractor by Working Day 10 of the following month. The sponsor also agreed to provide, in accordance with 21 CFR 600.80, the Quarterly Periodic Adverse Experience Report to the VAERS contractor. The Quarterly Adverse Experience Report will contain a recapitulation of all initial reports submitted for the current reporting period and will include all follow up information on VAERS forms collected during that three-month period. The sponsor has also committed to provide CBER this information using the aforementioned process, for the first three years after the date of licensure.

13.3 **Labeling**

There were multiple communications with the sponsor to work on the label in order to achieve consistency with CBER’s current guidance on the intent and format of package inserts.

- Efficacy in the MITT-3 population was included in the label
- Imune responses were clarified, and immune responses in males were not included in the label
- Only safety data from males were considered for the label

- Additional information on specific adverse events was included in the label

The final clean label was reviewed and found acceptable.

14. **Comments and questions for the applicant**

The sponsor provided responses to all reviewer questions during the course of the BLA review.