HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME (COVID-19 mRNA vaccine [nucleoside-modified]) suspension for intramuscular injection
Initial U.S. Approval: YYYY

----------INDICATIONS AND USAGE----------
TRADENAME is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in individuals 16 years of age and older (1)

----------DOSAGE AND ADMINISTRATION----------
TRADENAME is administered intramuscularly as a series of 2 doses (0 3 mL each) 3 weeks apart (2 3)

---------- DOSAGE FORMS AND STRENGTHS----------
Suspension for injection After preparation, a single dose is 0 3 mL (3)

----------CONTRAINDICATIONS ----------
Known history of a severe allergic reaction (e g , anaphylaxis) to any component of TRADENAME (4)

---------- WARNINGS AND PRECAUTIONS ----------
Recipients should be monitored for the occurrence of immediate allergic reactions including anaphylaxis (5 1)

----------ADVERSE REACTIONS----------
In clinical studies of participants 16 years of age and older, the most commonly reported adverse reactions (>10%) were pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, fever, and injection site swelling (6 1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS----------
Pediatric Use: Safety and effectiveness of TRADENAME in individuals younger than 16 years of age have not been established (8 4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: M/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

Commented [A1]: Module 5.3 5.1 Supplemental tables:

Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRADENAME is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

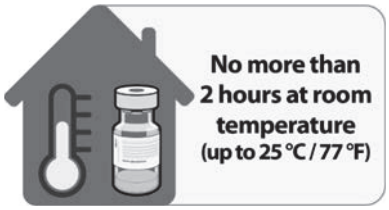
2.1 Preparation for Administration

Prior to Dilution

- TRADENAME Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *[see How Supplied/Storage and Handling (16)]*.
- Refer to thawing instructions in the panels below.

Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP to form TRADENAME. Do not add more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, 1 vial contains 6 doses of 0.3 mL.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of TRADENAME before use either by: ○ Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 5 days (120 hours). ○ Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

Commented [A2]: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4 (intro)

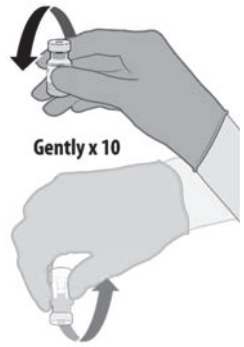
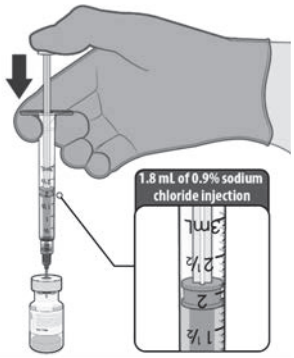
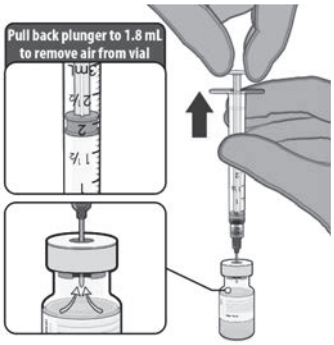
Commented [A3]: BLA Section 3.2 P 2 6, and 3 2.P.2 3 Manufacturing Process Development - Process Development and Characterization

Commented [A4]: BLA section 3.2.P.1 and 3.2.P 2.6

Commented [A5]: BLA section 3.2.P.2.6

Commented [A6]: BLA section 3.2.P.1, and 3 2.P.2 2

Commented [A7]: BLA Section 3.2 P 2 6 for all instructions for use

	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.
	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.

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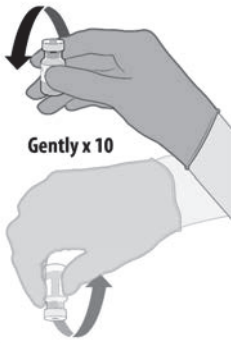
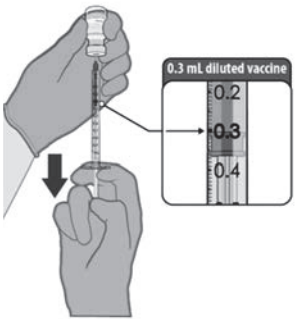
	• Gently invert the vial containing the TRADENAME 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the TRADENAME vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of TRADENAME preferentially using low dead-volume syringes and/or needles. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer TRADENAME intramuscularly.

After dilution, vials of TRADENAME contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle,

- each dose must contain 0.3 mL of vaccine.
- if the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- do not pool excess vaccine from multiple vials

2.3 Vaccination Schedule for Individuals 16 Years of Age and Older

TRADENAME is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart.

There are no data available on the interchangeability of TRADENAME with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of TRADENAME should receive a second dose of TRADENAME to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

TRADENAME is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer TRADENAME to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the TRADENAME *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

As with any vaccines, appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of TRADENAME.

Monitor TRADENAME recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis html).

Commented [A9]: BLA Section 3 2 P.2.6

Commented [A10]: BLA Section 3.2 P.2.6

Commented [A11]: BLA Section 3.2 P.1

Commented [A12]: BLA section 3.2.P.2.6

Commented [A13]: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4 (intro)

Commented [A14]: BLA Section 3.2 P.1

Commented [A15]: Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (AC P)

5.2 Concurrent Illness at Time of Vaccination

The administration of TRADENAME should be postponed in individuals suffering from acute severe febrile illness.

5.3 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the TRADENAME.

5.4 Bleeding Precautions

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

5.5 Limitation of Effectiveness

As with any vaccine, TRADENAME may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In clinical studies with a data cut-off of March 13, 2021, adverse reactions in participants 16 years of age and older included pain at the injection site (84.3%), fatigue (64.7%), headache (57.1%), muscle pain (40.2%), chills (34.7%), joint pain (25.0%), fever (15.2%), injection site swelling (11.1%), injection site redness (9.9%), nausea (1.2%), malaise (0.6%), lymphadenopathy (0.4%), asthenia (0.3%), decreased appetite (0.2%), hyperhidrosis (0.1%), lethargy (0.1%), and night sweats (0.1%).

Severe allergic reactions, including anaphylaxis, have been reported following administration of TRADENAME outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of TRADENAME was evaluated in participants 16 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, 2-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 46,000 participants, 12 years of age or older. Of these, approximately 44,047 participants (22,026 TRADENAME; 22,021 placebo) in Phase 2/3 are 16 years of age or older (including 378 and 376 adolescents 16 through 17 years of age in the vaccine and placebo groups, respectively). Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection; HIV-positive participants are included in safety population disposition but are summarized separately in safety analyses.

Commented [A16]: Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (AC P)

Commented [A17]: Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (AC P)

Commented [A18]: Module 5.3.5.1 Supplemental tables:

Local Reactions by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

C4591001 16+ 6-Mo Update CSR: Table 30. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Commented [A19]: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.1.1.1.2

Commented [A20]: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.1.1 2.2

Commented [A21]: C4591001 16+ 6-Mo Update CSR: Table 9 – Follow-up Time After Dose 2 – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

C4591001 16+ 6-Mo Update CSR: Supplemental Table 14 52 – Demographic Characteristics – Phase 2/3 Subjects ≥12 Years of Age – Safety Population

Commented [A22]: C4591001 16+ 6-Mo Update CSR: Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Commented [A23]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14 84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population

C4591001 16+ 6-Mo Update CSR, Section 10.1.2.2. Open-Label Follow-Up Period

At the time of the analysis of Study 2 for the Emergency Use Authorization (EUA) with a data cut-off of November 14, 2020, there were 37,586 participants (18,801 TRADENAME and 18,785 placebo) 16 years of age or older followed for a median of 2 months after the second dose of TRADENAME. At the time of the analysis of Study 2 for the EUA with a data cut-off of March 13, 2021, there were 25,651 (58.2%) participants (13,031 TRADENAME and 12,620 placebo) 16 years of age and older followed for ≥4 months after the second dose.

The safety evaluation in Study 2 is ongoing. The safety population includes participants enrolled by October 9, 2020, and includes safety data accrued through March 13, 2021. Participants 16 years and older in the reactogenicity subset are monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received TRADENAME and those who received placebo. Overall, among the total participants who received either TRADENAME or placebo, 50.9% were male and 49.1% were female, 82.0% were White, 9.6% were Black or African American, 25.9% were Hispanic/Latino, 4.3% were Asian, and 1.0% were American Indian or Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days following each dose of TRADENAME and placebo in the subset of participants 16 through 55 years of age included in the safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of TRADENAME and placebo for participants 56 years of age and older.

In participants 16 to 55 years of age after receiving Dose 2, the mean duration of pain at the injection site was 2.5 days (range 1 to 70 days), for redness 2.2 days (range 1 to 9 days), and for swelling 2.1 days (range 1 to 8 days) for participants in the TRADENAME group. In participants 56 years of age and older after receiving Dose 2, the mean duration of pain at the injection site was 2.4 days (range 1 to 36 days), for redness 3.0 days (range 1 to 34 days), and for swelling 2.6 days (range 1 to 34 days) for participants in the TRADENAME group.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

	TRADENAME Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	TRADENAME Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Redness[c]				
Any (>2.0 cm)	156 (5.4)	28 (1.0)	151 (5.6)	18 (0.7)
Mild	113 (3.9)	19 (0.7)	90 (3.4)	12 (0.4)
Moderate	36 (1.2)	6 (0.2)	50 (1.9)	6 (0.2)
Severe	7 (0.2)	3 (0.1)	11 (0.4)	0

Commented [A24]: C4591001 Final Analysis CSR, Section 12.3.3.1

Commented [A25]: C4591001 16+ 6-Mo Update CSR: Table 9 – Follow-up Time After Dose 2 – Phase 2/3 Subjects ≥16 Years of Age – Safety Population.

Commented [A26]: C4591001 16+ 6-Mo Update CSR, Section 9.1 2

Commented [A27]: C4591001 Final Analysis CSR, Section 12.3.3.1

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Commented [A31]: C4591001 16+ 6-Mo Update CSR, Section 10.5.2.1.1

Commented [A32]: C4591001 16+ 6-Mo Update CSR: Table 12 – Demographic Characteristics – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Commented [A33]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.70 – Duration (Days) From First to Last Day of Local Reactions, by Age Group (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Commented [A34]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14 68 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	TRADENAME Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	TRADENAME Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Swelling[c]				
Any (>2.0 cm)	184 (6.3)	16 (0.6)	183 (6.8)	5 (0.2)
Mild	124 (4.3)	6 (0.2)	110 (4.1)	3 (0.1)
Moderate	54 (1.9)	8 (0.3)	66 (2.5)	2 (0.1)
Severe	6 (0.2)	2 (0.1)	7 (0.3)	0
Pain at the injection site[d]				
Any	2426 (83.7)	414 (14.2)	2101 (78.3)	312 (11.6)
Mild	1464 (50.5)	391 (13.4)	1274 (47.5)	284 (10.6)
Moderate	923 (31.8)	20 (0.7)	788 (29.4)	28 (1.0)
Severe	39 (1.3)	3 (0.1)	39 (1.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination
No Grade 4 solicited local reactions were reported in participants 16 through 55 years of age

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention

a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose The N for each reaction was the same, therefore, this information was included in the column header

b n = Number of participants with the specified reaction

c Mild: >2 0 to ≤5 0 cm; Moderate: >5 0 to ≤10 0 cm; Severe: >10 0 cm

d Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

Commented [A35]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.75 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	TRADENAME Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	TRADENAME Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Fever				
≥38.0°C	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
≥38.0°C to 38.4°C	86 (3.0)	16 (0.6)	254 (9.5)	5 (0.2)
>38.4°C to 38.9°C	25 (0.9)	5 (0.2)	146 (5.4)	4 (0.1)
>38.9°C to 40.0°C	8 (0.3)	4 (0.1)	39 (1.5)	2 (0.1)
>40.0°C	0	0	1 (0.0)	0
Fatigue[c]				
Any	1431 (49.4)	960 (33.0)	1649 (61.5)	614 (22.9)
Mild	760 (26.2)	570 (19.6)	558 (20.8)	317 (11.8)
Moderate	630 (21.7)	372 (12.8)	949 (35.4)	283 (10.5)
Severe	41 (1.4)	18 (0.6)	142 (5.3)	14 (0.5)
Headache[c]				
Any	1262 (43.5)	975 (33.5)	1448 (54.0)	652 (24.3)
Mild	785 (27.1)	633 (21.8)	699 (26.1)	404 (15.1)
Moderate	444 (15.3)	318 (10.9)	658 (24.5)	230 (8.6)
Severe	33 (1.1)	24 (0.8)	91 (3.4)	18 (0.7)

	TRADENAME Dose 1 N[a]=2899 n[b] (%)	Placebo Dose 1 N[a]=2908 n[b] (%)	TRADENAME Dose 2 N[a]=2682 n[b] (%)	Placebo Dose 2 N[a]=2684 n[b] (%)
Chills[c]				
Any	479 (16.5)	199 (6.8)	1015 (37.8)	114 (4.2)
Mild	338 (11.7)	148 (5.1)	477 (17.8)	89 (3.3)
Moderate	126 (4.3)	49 (1.7)	469 (17.5)	23 (0.9)
Severe	15 (0.5)	2 (0.1)	69 (2.6)	2 (0.1)
Vomiting[d]				
Any	34 (1.2)	36 (1.2)	58 (2.2)	30 (1.1)
Mild	29 (1.0)	30 (1.0)	42 (1.6)	20 (0.7)
Moderate	5 (0.2)	5 (0.2)	12 (0.4)	10 (0.4)
Severe	0	1 (0.0)	4 (0.1)	0
Diarrhea[e]				
Any	309 (10.7)	323 (11.1)	269 (10.0)	205 (7.6)
Mild	251 (8.7)	264 (9.1)	219 (8.2)	169 (6.3)
Moderate	55 (1.9)	58 (2.0)	44 (1.6)	35 (1.3)
Severe	3 (0.1)	1 (0.0)	6 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	664 (22.9)	329 (11.3)	1055 (39.3)	237 (8.8)
Mild	353 (12.2)	231 (7.9)	441 (16.4)	150 (5.6)
Moderate	296 (10.2)	96 (3.3)	552 (20.6)	84 (3.1)
Severe	15 (0.5)	2 (0.1)	62 (2.3)	3 (0.1)
New or worsened joint pain[c]				
Any	342 (11.8)	168 (5.8)	638 (23.8)	147 (5.5)
Mild	200 (6.9)	112 (3.9)	291 (10.9)	82 (3.1)
Moderate	137 (4.7)	55 (1.9)	320 (11.9)	61 (2.3)
Severe	5 (0.2)	1 (0.0)	27 (1.0)	4 (0.1)
Use of antipyretic or pain medication[f]	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose

No Grade 4 solicited systemic reactions were reported in participants 16 through 55 years of age

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention

a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose The N for each reaction or use of antipyretic or pain medication was the same, therefore, this information was included in the column header

b n = Number of participants with the specified reaction

c Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity

d Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration

e Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours

f Severity was not collected for use of antipyretic or pain medication

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	TRADENAME Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	TRADENAME Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Redness[c]				
Any (>2.0 cm)	106 (5.3)	20 (1.0)	133 (7.2)	14 (0.8)
Mild	71 (3.5)	13 (0.7)	65 (3.5)	10 (0.5)
Moderate	30 (1.5)	5 (0.3)	58 (3.1)	3 (0.2)
Severe	5 (0.2)	2 (0.1)	10 (0.5)	1 (0.1)
Swelling[c]				
Any (>2.0 cm)	141 (7.0)	23 (1.2)	145 (7.8)	13 (0.7)
Mild	87 (4.3)	11 (0.6)	80 (4.3)	5 (0.3)
Moderate	52 (2.6)	12 (0.6)	61 (3.3)	7 (0.4)
Severe	2 (0.1)	0	4 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2.0 cm)	1408 (70.1)	185 (9.3)	1230 (66.1)	143 (7.8)
Mild	1108 (55.2)	177 (8.9)	873 (46.9)	138 (7.5)
Moderate	296 (14.7)	8 (0.4)	347 (18.7)	5 (0.3)
Severe	4 (0.2)	0	10 (0.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination
No Grade 4 solicited local reactions were reported in participants 56 years of age and older
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention
a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose The N for each reaction was the same, therefore, the information was included in the column header
b n = Number of participants with the specified reaction
c Mild: >2 0 to ≤5 0 cm; Moderate: >5 0 to ≤10 0 cm; Severe: >10 0 cm
d Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	TRADENAME Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	TRADENAME Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Fever				
≥38.0°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4°C to 38.9°C	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9°C to 40.0°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0°C	0	0	0	0
Fatigue[c]				
Any	677 (33.7)	447 (22.5)	949 (51.0)	306 (16.7)
Mild	415 (20.7)	281 (14.1)	391 (21.0)	183 (10.0)
Moderate	259 (12.9)	163 (8.2)	497 (26.7)	121 (6.6)
Severe	3 (0.1)	3 (0.2)	60 (3.2)	2 (0.1)
Grade 4	0	0	1 (0.1)	0

Commented [A36]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14 68 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

Commented [A37]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.75 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group (Reactogenicity Subset) – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

	TRADENAME Dose 1 N[a]=2008 n[b] (%)	Placebo Dose 1 N[a]=1989 n[b] (%)	TRADENAME Dose 2 N[a]=1860 n[b] (%)	Placebo Dose 2 N[a]=1833 n[b] (%)
Headache[c]				
Any	503 (25.0)	363 (18.3)	733 (39.4)	259 (14.1)
Mild	381 (19.0)	267 (13.4)	464 (24.9)	189 (10.3)
Moderate	120 (6.0)	93 (4.7)	256 (13.8)	65 (3.5)
Severe	2 (0.1)	3 (0.2)	13 (0.7)	5 (0.3)
Chills[c]				
Any	130 (6.5)	69 (3.5)	435 (23.4)	57 (3.1)
Mild	102 (5.1)	49 (2.5)	229 (12.3)	45 (2.5)
Moderate	28 (1.4)	19 (1.0)	185 (9.9)	12 (0.7)
Severe	0	1 (0.1)	21 (1.1)	0
Vomiting[d]				
Any	10 (0.5)	9 (0.5)	13 (0.7)	5 (0.3)
Mild	9 (0.4)	9 (0.5)	10 (0.5)	5 (0.3)
Moderate	1 (0.0)	0	1 (0.1)	0
Severe	0	0	2 (0.1)	0
Diarrhea[e]				
Any	168 (8.4)	130 (6.5)	152 (8.2)	102 (5.6)
Mild	137 (6.8)	109 (5.5)	125 (6.7)	76 (4.1)
Moderate	27 (1.3)	20 (1.0)	25 (1.3)	22 (1.2)
Severe	4 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	274 (13.6)	165 (8.3)	537 (28.9)	99 (5.4)
Mild	183 (9.1)	111 (5.6)	229 (12.3)	65 (3.5)
Moderate	90 (4.5)	51 (2.6)	288 (15.5)	33 (1.8)
Severe	1 (0.0)	3 (0.2)	20 (1.1)	1 (0.1)
New or worsened joint pain[c]				
Any	175 (8.7)	124 (6.2)	353 (19.0)	72 (3.9)
Mild	119 (5.9)	78 (3.9)	183 (9.8)	44 (2.4)
Moderate	53 (2.6)	45 (2.3)	161 (8.7)	27 (1.5)
Severe	3 (0.1)	1 (0.1)	9 (0.5)	1 (0.1)
Use of antipyretic or pain medication[f]	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose

The only Grade 4 solicited systemic reaction reported in participants 56 years of age and older was fatigue

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention

a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose N for each reaction or use of antipyretic or pain medication was the same, therefore was included in the column header

b n = Number of participants with the specified reaction

c Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity; Grade 4 reactions were defined in the clinical study protocol as emergency room visit or hospitalization for severe fatigue, severe headache, severe chills, severe muscle pain, or severe joint pain

d Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration; Grade 4 emergency visit or hospitalization for severe vomiting

e Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours; Grade 4: emergency room or hospitalization for severe diarrhea

f Severity was not collected for use of antipyretic or pain medication

Table 5 and Table 6 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of TRADENAME and placebo for participants 16 years of age and older with confirmed stable HIV infection.

Table 5: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Redness[c]				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling[c]				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0
Pain at the injection site[d]				
Any	34 (63.0)	9 (16.1)	32 (53.3)	5 (8.1)
Mild	26 (48.1)	8 (14.3)	22 (36.7)	5 (8.1)
Moderate	8 (14.8)	1 (1.8)	9 (15.0)	0
Severe	0	0	1 (1.7)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination
No Grade 4 solicited local reactions were reported in HIV-positive participants 16 years of age and older
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention
a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose The N for each reaction was the same, therefore, this information was included in the column header
b n = Number of participants with the specified reaction
c Mild: >2 0 to ≤5 0 cm; Moderate: >5 0 to ≤10 0 cm; Severe: >10 0 cm
d Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

Table 6: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – HIV-Positive Participants 16 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fever				
≥38.0°C	1 (1.9)	4 (7.1)	9 (15.0)	5 (8.1)
≥38.0°C to 38.4°C	1 (1.9)	2 (3.6)	4 (6.7)	5 (8.1)
>38.4°C to 38.9°C	0	0	4 (6.7)	0
>38.9°C to 40.0°C	0	2 (3.6)	1 (1.7)	0
>40.0°C	0	0	0	0

Commented [A38]: C4591001 16+ 6-Mo Update CSR Supplemental table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

Commented [A39]: C4591001 16+ 6-Mo Update CSR Supplemental table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)
Fatigue[c]				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache[c]				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills[c]				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0
Vomiting[d]				
Any	1 (1.9)	3 (5.4)	2 (3.3)	2 (3.2)
Mild	1 (1.9)	1 (1.8)	1 (1.7)	1 (1.6)
Moderate	0	0	1 (1.7)	1 (1.6)
Severe	0	2 (3.6)	0	0
Diarrhea[c]				
Any	5 (9.3)	8 (14.3)	4 (6.7)	9 (14.5)
Mild	5 (9.3)	6 (10.7)	1 (1.7)	6 (9.7)
Moderate	0	1 (1.8)	2 (3.3)	3 (4.8)
Severe	0	1 (1.8)	1 (1.7)	0
New or worsened muscle pain[c]				
Any	9 (16.7)	10 (17.9)	10 (16.7)	5 (8.1)
Mild	7 (13.0)	7 (12.5)	5 (8.3)	1 (1.6)
Moderate	2 (3.7)	3 (5.4)	5 (8.3)	4 (6.5)
Severe	0	0	0	0
New or worsened joint pain[c]				
Any	5 (9.3)	7 (12.5)	10 (16.7)	5 (8.1)
Mild	5 (9.3)	4 (7.1)	4 (6.7)	1 (1.6)
Moderate	0	3 (5.4)	6 (10.0)	4 (6.5)
Severe	0	0	0	0
Use of antipyretic or pain medication[f]	7 (13.0)	8 (14.3)	16 (26.7)	7 (11.3)

Notes: Reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose

No Grade 4 solicited systemic reactions were reported in HIV-positive participants 16 years of age and older

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention

a N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose The N for each event or use of antipyretic or pain medication was the same, therefore, this information was included in the column header

b n = Number of participants with the specified reaction

c Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity

d Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration

	TRADENAME Dose 1 N[a]=54 n[b] (%)	Placebo Dose 1 N[a]=56 n[b] (%)	TRADENAME Dose 2 N[a]=60 n[b] (%)	Placebo Dose 2 N[a]=62 n[b] (%)

e Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours
f Severity was not collected for use of antipyretic or pain medication

Unsolicited Adverse Events

Upon approval of the EUA for TRADENAME, participants were unblinded to offer placebo participants TRADENAME. Adverse events are reported as incidence rates per 100 person-years to account for the variable exposure since unblinding began in a phased manner for participants in the study. Adverse events detailed below for participants 16 years of age and older are for the placebo-controlled blinded follow-up period up to the participants' unblinding dates.

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (TRADENAME =12,995; placebo = 13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported at an incidence rate of 2.1 per 100 person-years among TRADENAME recipients and 2.4 per 100 person-years among placebo recipients. In a similar analysis, in participants 56 years of age and older (TRADENAME =8931, placebo = 8895), serious adverse events were reported at an incidence rate of 4.9 per 100 person-years among TRADENAME recipients and 4.6 per 100 person-years among placebo recipients who received at least 1 dose of TRADENAME or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after Dose 2. Among participants with confirmed stable HIV infection serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported at an incidence rate of 6.6 per 100 person-years among TRADENAME recipients and 6.9 per 100 person-years among placebo recipients.

There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to TRADENAME.

Non-Serious Adverse Events

Overall in Study 2 in which 12,995 participants 16 through 55 years of age received TRADENAME and 13,026 participants received placebo, all events, which include non-serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported at an incidence rate of 88.4 per 100 person-years among participants who received TRADENAME and 43.5 per 100 person-years among participants in the placebo group, for participants who received at least 1 dose. In a similar analysis, in participants 56 years of age and older (TRADENAME = 8931, placebo = 8895), all events, which include non-serious adverse events were reported at an incidence rate of 75.7 per 100 person-years among participants who received TRADENAME and 43.3 per 100 person-years among participants in the placebo group, for participants who received at least 1 dose. Among participants with confirmed stable HIV infection, all events, which include non-serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported at an incidence rate of 95.8 per 100 person-years among participants who received

Commented [A40]: C4591001 CSR Section 12.2.3 Adverse Events – Phase 2/3 Participants ≥16 Years of Age

Commented [A41]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.106. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by Age Group – Phase 2/3 Subjects ≥16 Years of Age – Safety Population Age Group: 16-55 Years

Commented [A42]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.107. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by Age Group – Phase 2/3 Subjects ≥16 Years of Age – Safety Population Age Group: >55 Years

Commented [A43]: C4591001 16+ 6-Mo Update CSR: Table 9 – Follow-up Time After Dose 2 – Phase 2/3 Subjects ≥16 Years of Age – Safety Population.

Commented [A44]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.179. Incidence Rates of at Least 1 Serious Adverse Event From Dose 1 to Unblinding Date, by System Organ Class and Preferred Term – Blinded Placebo – Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

Commented [A45]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.106. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by Age Group – Phase 2/3 Subjects ≥16 Years of Age – Safety Population Age Group: 16-55 Years

Commented [A46]: C4591001 16+ 6-Mo Update CSR: Supplemental table 14.107. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date, by Age Group – Phase 2/3 Subjects ≥16 Years of Age – Safety Population Age Group: >55 Years

TRADENAME and 52.0 per 100 person-years among participants in the placebo group, for participants who received at least 1 dose.

In these analyses, 58.2% of study participants had at least 4 months of follow-up after Dose 2. The higher frequency of reported unsolicited non-serious adverse events among TRADENAME recipients (inclusive of stable HIV infection) compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following each dose of vaccine that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Table 3 and Table 4.

Throughout the placebo-controlled safety follow-up period to date, Bell's palsy (facial paralysis) was reported by 4 participants in the TRADENAME group and 2 participants in the placebo group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. In the placebo group the onset of facial paralysis was Day 32 and Day 102. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to TRADENAME.

Commented [A47]: C4591001 16+ 6-Mo Update CS: Supplemental table 14.118. Incidence Rates of at Least 1 Adverse Event From Dose 1 to Unblinding Date – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population

Commented [A48]: C4591001 16+ 6-Mo Update CSR: Table 9 – Follow-up Time After Dose 2 – Phase 2/3 Subjects ≥16 Years of Age – Safety Population.

Commented [A49]: C4591001 16+ 6-Mo Update CSR, Section 14 Tables and Figures, Subject Narratives, Bell's Palsy.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post authorization use of TRADENAME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Commented [A50]: Mod 2.7.4 Summary of Clinical Safety, Section 2.7.4.2.4 3.5

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Gastrointestinal Disorders: diarrhea, vomiting
Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

7 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the TRADENAME with other vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Commented [A51]: Module 2.4 Nonclinical Overview, Section 2.4.4.6

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on TRADENAME administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Data

Animal Data

In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of TRADENAME was administered to female rats by the intramuscular route on

4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

8.2 Lactation

Risk Summary

It is not known whether TRADENAME is excreted in human milk. Data are not available to assess the effects of TRADENAME on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety and effectiveness of TRADENAME in individuals younger than 16 years of age have not been established.

8.5 Geriatric Use

Of the total number of TRADENAME recipients in Study 2 as of March 13, 2021 (N = 22,026), 20.7% (n = 4552) were 65 years of age and older and 4.2% (n = 925) were 75 years of age and older *[see Clinical Studies (14.1)]*. The safety and effectiveness in geriatric participants was consistent with that seen in younger adult participants.

Commented [A52]: C4591001 C4591001 16+ 6-Mo Update CSR, Supplemental Table 14.198. Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population

10 OVERDOSAGE

Participants who received 58 micrograms of TRADENAME in clinical trials did not report an increase in reactogenicity or adverse events.

Commented [A53]: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.3 5

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

11 DESCRIPTION

TRADENAME is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of TRADENAME contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the TRADENAME also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

Commented [A54]: BLA section 3.2.P.1

TRADENAME does not contain preservative. The vial stoppers are not made with natural rubber latex.

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Commented [A56]: BLA section 3.2.P.2.4

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The modRNA in TRADENAME is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TRADENAME has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In studies in rats with TRADENAME, there were no vaccine-related effects on female fertility *[see Use in Special Populations (8.1)]*.

14 CLINICAL STUDIES

14.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion of Study 2, based on data accrued through November 14, 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of TRADENAME or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the TRADENAME group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. Table 7 presents the specific demographic characteristics in the studied population.

Commented [A57]: Module 2.5 Clinical Overview, Section 2 5.1.2.2

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Commented [A59]: C4591001 16+ 6-Mo Update CSR, Section 9.1 2

Commented [A60]: C4591001 Final Analysis CSR, Section 9.3.2

Commented [A61]: Module 2.7 3 (SCE) Section 2.7.3.1.1 2 Module 2.7.3 (SCE) Section 2.7 3.1.1 2.2

Commented [A62]: C4591001 Final Analysis CSR: Supplemental Table 14.256. Disposition of All Randomized Subjects – Phase 2/3(All Subjects):

Commented [A63]: Final Analysis Interim CSR (Nov 14, 2020 data cutoff) that was filed to the ND and referenced in the original EUA submission in November 2020.

Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

Section 10.4.3.3 Efficacy Populations – Final Analysis, Table 13 Efficacy Populations

Commented [A64]: Module 2.5 Clinical Overview, Section 2 5.1.2.3.2 2

Commented [A65]: C4591001 Final Analysis CSR: Table 18 Demographic Characteristics – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Table 7: Demographics (Population For the Primary Efficacy Endpoint)[a]

	TRADENAME (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2

b Includes multiracial and not reported

c Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease:

- Chronic lung disease (e g , emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e g , heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Obesity (body mass index ≥30 kg/m^2)
- Diabetes (Type 1, Type 2, or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Efficacy Against COVID-19

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 through 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 through 17 years of age began enrollment from September 16, 2020, and 12 through 15 years of age began enrollment from October 15, 2020.

Commented [A66]: C4591001 Final Analysis CSR, Section 7

The vaccine efficacy information is presented in Table 8.

Table 8: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**TRADENAME Na=18,198 Cases n1b Surveillance Timec (n2d)**	**Placebo Na=18,325 Cases n1b Surveillance Timec (n2d)**	**Vaccine Efficacy % (95% CI)**
All participantse	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)f
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)g
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)g
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)g
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)g
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	**TRADENAME Na=19,965 Cases n1b Surveillance Timec (n2d)**	**Placebo Na=20,172 Cases n1b Surveillance Timec (n2d)**	**Vaccine Efficacy % (95% CI)**
All participantse	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)f
16 to 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)g
65 years and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)g
65 to 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)g
75 years and older	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)g

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = Number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

d n2 = Number of participants at risk for the endpoint

Commented [A67]: C4591001 Final Analysis CSR: Table 34. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Commented [A68]: Module 5.3 5.1 Ad Hoc Label Tables: Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2 by Requested Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Commented [A69]: Module 5.3 5.1 Ad Hoc Label Tables: Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

e No confirmed cases were identified in participants 12 to 15 years of age
f Two-sided credible interval for vaccine efficacy was calculated using a beta-binomial model with a beta (0 700102, 1) prior for θ=r(1-VE)/(1+r(1-VE)), where r is the ratio of surveillance time in the active vaccine group over that in the placebo group
g Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information is presented in Table 9.

Table 9: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

Commented [A70]: C4591001 16+ 6-Mo Update CSR, Section 11.1.2 and Figure 2

Commented [A71]: C4591001 16+ 6-Mo Update CSR: Table 19. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Commented [A72]: C4591001 16+ 6-Mo Update CSR CSR: Supplemental Table 14.59. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = Number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

d n2 = Number of participants at risk for the endpoint

e Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

f Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively)

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 10 and Table 11.

Table 10: Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10,075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others[f]	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)

Commented [A73]: C4591001 16+ 6-Mo Update CSR: Table 19. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)
Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = Number of participants in the specified group
b n1 = Number of participants meeting the endpoint definition
c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period
d n2 = Number of participants at risk for the endpoint
e Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time
f All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories

Table 11: Vaccine Efficacy– First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Commented [A74]: C4591001 16+ 6-Mo Update CSR: Supplemental Table 14.59. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = Number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

d n2 = Number of participants at risk for the endpoint

e Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

f All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories

The updated subgroup analyses of vaccine efficacy by risk status in participants are presented in Table 12 and Table 13.

Table 12: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk[g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese[h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = Number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

d n2 = Number of participants at risk for the endpoint

e Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time

f Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group

Commented [A75]: C4591001 16+ 6-Mo Update CSR: Table 20. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

g At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age])

h Obese is defined as BMI ≥30 kg/m^2 For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm

Table 13: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Commented [A76]: C4591001 16+ 6-Mo Update CSR: Table 21. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk[g]			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese[h]			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

Table 13: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

a N = number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

c Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

d n2 = Number of participants at risk for the endpoint

e Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time

f Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group

g At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 years of age])

h Obese is defined as BMI ≥30 kg/m^2 For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile Refer to the CDC growth charts at https://www cdc gov/growthcharts/html_charts/bmiagerev htm

Commented [A76]: C4591001 16+ 6-Mo Update CSR: Table 21. Vaccine Efficacy – First COV D-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Against Severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of TRADENAME in preventing severe COVID-19. Vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 14) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the TRADENAME and placebo groups.

Commented [A77]: C4591001 16+ 6-Mo Update CSR: Table 24. Vaccine Efficacy – First Severe COV D-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Table 14: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	Placebo Cases n1[a] Surveillance Time (n2[b])	Vaccine Efficacy % (95% CI[c])
After Dose 1[d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)

Commented [A78]: C4591001 CSR Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

C4591001 CSR Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	Placebo Cases n1[a] Surveillance Time (n2[b])	Vaccine Efficacy % (95% CI[c])
After Dose 1[d]	1 8.427[e] (22,473)	45 8.269[e] (22,394)	97.8 (87.2, 99.9)
7 days after Dose 2[f]	0 6.514[g] (21,620)	32 6.391[g] (21,693)	100 (88.0, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting)

* Participants who had no evidence of past SARS-CoV-2 infection (i e , N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis

[f] Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death

[g] Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death

a n1 = Number of participants meeting the endpoint definition

b n2 = Number of participants at risk for the endpoint

c Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

d Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomized participants who received at least 1 dose of study intervention

e Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period

f Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomized participants who receive all dose(s) of study intervention as randomized within the predefined window, have no other important protocol deviations as determined by the clinician

g Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 0069-1000-03) or 195 multiple dose vials (NDC 0069-1000-02). A 0.9% Sodium Chloride Injection, USP diluent is supplied separately. After dilution, 1 vial contains 6 doses of 0.3 mL.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light

Do not refreeze thawed vials.

Commented [A79]: C4591001 CSR Supplemental Table 14 61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

C4591001 CSR Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Commented [A80]: US Food and Drug Administration. Development and Licensure of Vaccines to Prevent COV D-19. Guidance for Industry. June 2020. Available at: https://www.fda gov/media/139638/download

Commented [A81]: Centers for Disease Control and Prevention (CDC). Coronavirus Disease (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html Accessed 09 December 2020.

Commented [A82]: C4591001 16+ 6-mo Update CSR Table 4

Commented [A83]: C4591001 16+ 6-mo Update CSR Table 4

Commented [A84]: BLA section 3.2.P.2.3 Manufacturing Process Development - Process Development and Characterization

Commented [A85]: BLA section 3.2.P.2.6 and 3 2.P.8 3 Photostability

Commented [A86]: BLA section 3.2.P.2.6

Frozen Vials Prior to Use

Cartons of TRADENAME Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF) until the expiry date printed on the label. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned 1 time to the recommended storage condition of -80ºC to -60ºC (-112ºF to -76ºF). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

Commented [A87]: BLA section 3.2.P.2.3 Manufacturing Process Development- Process Development and Characterization

Commented [A88]: BLA section 3.2.P.8

If an ultra-low temperature freezer is not available, the thermal container in which TRADENAME arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Commented [A89]: BLA section 3.2.P.3.5 Shipping Validation

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned 1 time to the recommended storage condition of -80ºC to -60ºC (-112ºF to -76ºF).

Commented [A90]: BLA section 3.2.P.3.5 Shipping Validation

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25ºC (77ºF)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Commented [A91]: BLA section 3.2.P.2.6 and 3 2.P.8 3 Stability Data - Accelerated

Transportation of Thawed Vials

Available data support transportation of 1 or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours. Any hours used for transport at 2°C to 8°C (35°F to 46°F) count against the 120-hour limit for storage at 2°C to 8°C (35°F to 46°F)

Commented [A92]: BLA section 3.2.P.3.5 Shipping Validation

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

Commented [A93]: BLA section 3.2.P.2.6

17 PATIENT COUNSELING INFORMATION

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about html.

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

Pfizer
Manufactured by
Pfizer Inc., New York, NY 10017

LAB-1448-0.1

US Govt. License No. x

Commented [A94]: Pfizer proposes to include the license number upon availability.

CPT Code x

Commented [A95]: Pfizer proposes to include the CPT code upon availability.