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

**COMIRNATY (COVID-19 Vaccine, mRNA) suspension for injection, for intramuscular use**
**Initial U.S. Approval: YYYY**

**---------- INDICATIONS AND USAGE ----------**
COMIRNATY 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 ----------**
- For intramuscular injection ~~administration~~ only (2 [2])
- COMIRNATY 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 COMIRNATY (4)

**---------- WARNINGS AND PRECAUTIONS ----------**
- Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose (5 2)
- Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY Procedures should be in place to avoid injury from fainting (5 4)

**---------- ADVERSE REACTIONS ----------**
- In clinical studies of participants 16 through 55 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)
- In clinical studies of participants 56 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, injection site swelling, fever, and injection site redness (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.**

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: M/YYYY**

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

**Commented [A2]:** Pfizer-BioNTech accepts FDA revision.

**Commented [A3]:** FDA comment
Pfizer,
Please see section 6 for a statement to include in highlights.

Pfizer-BioNTech response
The Sponsor accepts and has included the listing of adverse reactions occurring at >10% in participants 16-55 years of age and 56 years of age and older.

**Commented [A1]:** Pfizer-BioNTech proposes to revise for consistency with FPI.

**Commented [A4]:** FDA comment
Pfizer,
Please make table of contents consistent with Full PI.

Pfizer-BioNTech response
The Sponsor accepts and has revised the table of contents consistent with the Full Prescribing Information.

**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

COMIRNATY 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

Commented [A5]: Pfizer-BioNTech accepts FDA revisions to this section.

### 2.1 Preparation for Administration

Prior to Dilution

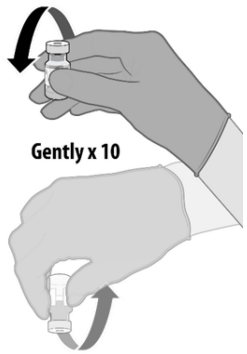
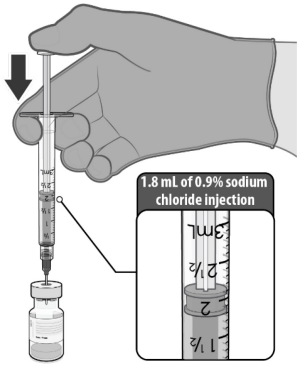
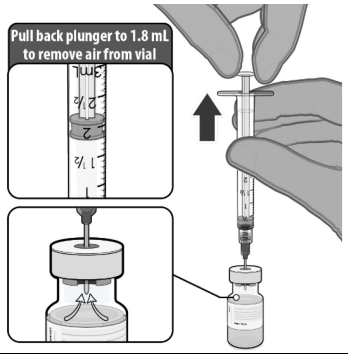
- COMIRNATY Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)]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

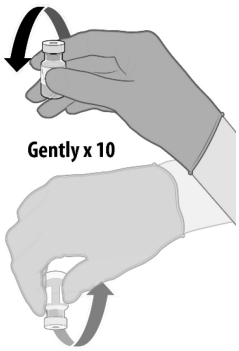
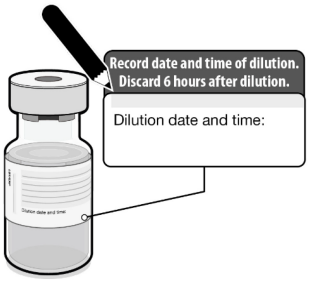
Dilution

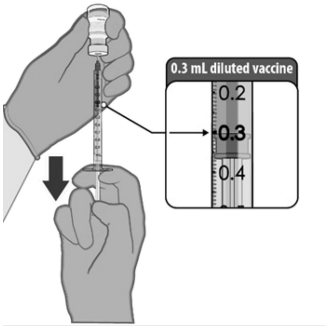
- Dilute the vial contents using 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP to form COMIRNATY. Do not add more than 1.8 mL of diluent.
- ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. Use the provided diluent or an alternate brand of sterile 0.9% Sodium Chloride Injection, USP as the diluent.
- Provided diluent vials are single-use only and should be discarded after 1.8 mL is withdrawn. Do not use provided diluent vials to dilute multiple vials of COMIRNATY.
- After dilution, 1 vial contains 6 doses of 0.3 mL each.
- Refer to dilution and dose preparation instructions in the panels below.

Commented [A6]: Pfizer BioNTech proposes to add this information to address the query received separately from CBER related to the number of uses of provided diluent vials.

| THAWING PRIOR TO DILUTION | |
|---|---|
|  | • Thaw vial(s) of COMIRNATY before dilution either by:<br>o Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month.<br>o Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.<br>• Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours. |

| | |
|---|---|
|  | • Before dilution invert vaccine vial gently 10 times.<br>• Do not shake.<br>• 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.<br>• Do not use if liquid is discolored or if other particles are observed. |
| **DILUTION** | |
|  | • ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent.<br>• Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).<br>• Cleanse the vaccine vial stopper with a single-use antiseptic swab.<br>• Add 1.8 mL of sterile 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. |

| | |
|---|---|
|  | • Gently invert the vial containing the COMIRNATY 10 times to mix.<br>• Do not shake.<br>• Inspect the vaccine in the vial.<br>• 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 COMIRNATY vial label.<br>• Store between 2°C to 25°C (35°F to 77°F).<br>• Discard any unused vaccine 6 hours after dilution. |

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

### 2.2 Administration Information

For intramuscular injection only.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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.

After dilution, vials of COMIRNATY 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

COMIRNATY 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 COMIRNATY with other COVID-19 vaccines to complete the vaccination series. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the vaccination series.

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of COMIRNATY.

### 5.2 Myocarditis and Pericarditis

Commented [A7]: Pfizer-BioNTech accepts FDA revisions to this subsection.

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk has been highest in adolescent and young adult males under 40 years of age. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms. Information is not yet available about potential long-term sequelae. The CDC has published

considerations for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis html).

### 5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY. Procedures should be in place to avoid injury from fainting.

### 5.4 Altered Immunocompetence

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

### 5.5 Limitation of Effectiveness

COMIRNATY may not protect all vaccine recipients.

## 6 ADVERSE REACTIONS

In clinical studies with a data cut-off of March 13, 2021, the most commonly reported (≥10%) adverse reactions in participants 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%).

In clinical studies with a data cut-off of March 13, 2021, the most commonly reported (≥10%) adverse reactions in participants 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

In clinical studies with a data cut-off of March 13, 2021, the adverse reactions occurring in <10% of participants 16 through 55 years of age following any dose were injection site redness (9.5%), nausea (1.4%), malaise- (0.7%), lymphadenopathy (0.5%), asthenia (0.4%), decreased appetite (0.2%), hyperhidrosis (0.1%), lethargy (0.1%), and night sweats (0.1%).

In clinical studies with a data cut-off of March 13, 2021, the adverse reactions occurring in <10% of participants 56 years of age and older following any dose were nausea (1.0%), malaise (0.5%), asthenia (0.3%), lymphadenopathy (0.2%), lethargy (0.2%), decreased appetite (0.1%), hyperhidrosis (0.1%), and night sweats (0.1%).

### 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 COMIRNATY was evaluated in participants 16 years of age and older in 2 clinical studies conducted in Germany (Study 1), United States, Argentina, Brazil, Turkey, South Africa, and Germany (Study 2). Study BNT162-01 (Study 1) was a Phase 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 multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine

**Commented [A8]: Pfizer-BioNTech** accepts FDA deletion of this information "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 COMIRNATY outside of clinical trials " and has provided updated proposal below

**Commented [A9]: FDA comment**
Pfizer,
Please complete the sentences and include in the Highlights.

**Pfizer-BioNTech response**
The Sponsor accepts and has updated the text as requested in section 6 of the Full Prescribing Information and in the Highlights page. The Sponsor has revised the FDA proposed text to list the adverse reactions by "≥" 10%. The Sponsor has also included the adverse reactions reported <10% by participants 16 to 55 years of age and 56 years of age and older.

candidate-selection and efficacy study that has enrolled approximately 44,047 participants (22,026 ~~TRADENAME~~COMIRNATY; 22,021 placebo) 16 years of age or older (including 378 and 376 participants 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. Confirmed stable HIV infection~~disease~~ was defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm$^3$ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

At the time of the analysis of the ongoing Study 2 with a data cut-off of March 13, 2021, there were 25,651 (58.2%) participants (13,031 COMIRNATY and 12,620 placebo) 16 years of age and older followed for ≥4 months after the second dose.

Participants 16 years and older in the reactogenicity subset were 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 COMIRNATY and those who received placebo. Overall, among the total participants who received either COMIRNATY or placebo, 50.9% were male, 49.1% were female, 79.3% were 16 through 64 years of age, 20.7% were ≥65 years of age and older, 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 COMIRNATY 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 COMIRNATY and placebo for participants 56 years of age and older.

In participants 16 ~~to~~ through 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 COMIRNATY 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 COMIRNATY group.

**Commented [A10]:** **Pfizer BioNTech** agrees with the minor FDA revisions to this section with one modification to update TRADENAME to Comirnaty.

**Commented [A11]:** **Pfizer BioNTech** proposes to modify for consistency throughout the label.

**Commented [A12]:** **Pfizer BioNTech** accepts FDA addition of this statement.

**Commented [A13]:** **Pfizer BioNTech** agrees with FDA deletion of the following statement "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 COMIRNATY and 18,785 placebo) 16 years of age or older followed for a median of 2 months after the second dose of COMIRNATY," as well as the minor modifications to this paragraph.

**Commented [A14]:** **Pfizer BioNTech** agrees with FDA deletion of the following statement "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 "

**Commented [A15]:** **FDA comment**
Pfizer: Please also include the age demographics for percentages of participants who are 16 through 64 years and ≥65 years of age.

**Pfizer-BioNTech response**
Pfizer has updated the label as per FDA request.
Source: Table E Demographics and Other Baseline Characteristics, Phase 2/3 Participants 16 Years of Age and Older, Through Data Cutoff March 13, 2021, Safety Population in label bundle, age group >=65 years row.

**Commented [A16]:** **Pfizer BioNTech** proposes to modify for consistency throughout the label.

**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***

| | COMIRNATY Dose 1 N[a]=2899 n[b] (%) | Placebo Dose 1 N[a]=2908 n[b] (%) | COMIRNATY 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 |
| 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 Participants with chronic, stable HIV infection were excluded

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***

| | COMIRNATY Dose 1 N[a]=2899 n[b] (%) | Placebo Dose 1 N[a]=2908 n[b] (%) | COMIRNATY 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) |

**Commented [A17]:** Pfizer: Please add footnotes to Tables 1-4, that participants with chronic, stable HIV disease were excluded.

**Pfizer-BioNTech response**
The Sponsor accepts and has added the footnote to Tables 1-4.

| | COMIRNATY Dose 1 N[a]=2899 n[b] (%) | Placebo Dose 1 N[a]=2908 n[b] (%) | COMIRNATY Dose 2 N[a]=2682 n[b] (%) | Placebo Dose 2 N[a]=2684 n[b] (%) |
|---|---|---|---|---|
| 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) |
| 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 Participants with chronic, stable HIV infection were excluded

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***

| | COMIRNATY Dose 1 N[a]=2008 n[b] (%) | Placebo Dose 1 N[a]=1989 n[b] (%) | COMIRNATY 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 Participants with chronic, stable HIV infection were excluded

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***

| | COMIRNATY Dose 1 N[a]=2008 n[b] (%) | Placebo Dose 1 N[a]=1989 n[b] (%) | COMIRNATY 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 |

| | COMIRNATY Dose 1 N[a]=2008 n[b] (%) | Placebo Dose 1 N[a]=1989 n[b] (%) | COMIRNATY Dose 2 N[a]=1860 n[b] (%) | Placebo Dose 2 N[a]=1833 n[b] (%) |
|---|---|---|---|---|
| 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 |
| 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[c] | | | | |
| 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 Participants with chronic, stable HIV infection were excluded

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

| | COMIRNATY Dose 1 N[a]=2008 n[b] (%) | Placebo Dose 1 N[a]=1989 n[b] (%) | COMIRNATY Dose 2 N[a]=1860 n[b] (%) | Placebo Dose 2 N[a]=1833 n[b] (%) |
|---|---|---|---|---|

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 COMIRNATY and placebo for participants 16 years of age and older with confirmed stable HIV infection.~~

In participants with chronic, stable HIV infection after receiving Dose 2, local reactions and systemic events were similar to those observed for all participants 16 years of age and older by severity, onset day, and median duration. The frequency of pain at the injection site was similar after Dose 1 compared with Dose 2 of COMIRNATY (63.0% versus 53.3%). The frequency of redness and swelling was similar after Dose 1 compared with Dose 2 of COMIRNATY (redness: 3.7% versus 6.7%; swelling: 5.6% versus 8.3%, respectively). There was 1 (1.7%) severe reaction (pain at the injection site) reported after Dose 2 of COMIRNATY and no Grade 4 local reactions were reported. Fever, headache, chills, and joint pain increased in frequency from Dose 1 to Dose 2 while fatigue, vomiting, diarrhea, and muscle pain were similar after each dose of COMIRNATY. There were no severe systemic events after Dose 1 of COMIRNATY but after Dose 2, there was 1 (1.7%) severe fever (>38.9°C to 40.0°C), 3 (5.0%) participants with severe fatigue, 2 (3.3%) participants with severe headache, 1 (1.7%) participant with severe chills, and 1 (1.7%) participant with severe diarrhea. There were no Grade 4 systemic events reported after either dose.

**Commented [A18]:** Pfizer: Please describe local and systemic reactogenicity for the stable, chronic HIV+ participants in text to indicate that the frequencies of local and solicited reactions were generally the same or less frequent as compared to the overall safety population described in Tables 1-4.

**Pfizer-BioNTech response**
The Sponsor accepts deletion of the 2 HIV tables and has proposed summary text.

~~**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***~~

| | ~~COMIRNATY Dose 1 N[a]=54 n[b] (%)~~ | ~~Placebo Dose 1 N[a]=56 n[b] (%)~~ | ~~COMIRNATY Dose 2 N[a]=60 n[b] (%)~~ | ~~Placebo Dose 2 N[a]=62 n[b] (%)~~ |
|---|---|---|---|---|
| ~~Redness[e]~~ | | | | |
| ~~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[e]~~ | | | | |
| ~~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~~ |

| | COMIRNATY Dose 1 N[a]=54 n[b] (%) | Placebo Dose 1 N[a]=56 n[b] (%) | COMIRNATY Dose 2 N[a]=60 n[b] (%) | Placebo Dose 2 N[a]=62 n[b] (%) |
|---|---|---|---|---|
| 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***

| | COMIRNATY Dose 1 N[a]=54 n[b] (%) | Placebo Dose 1 N[a]=56 n[b] (%) | COMIRNATY 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 |
| Fatigue[e] | | | | |
| 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[e] | | | | |
| 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[e] | | | | |
| 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 |

| | COMIRNATY Dose 1 N[a]=54 n[b] (%) | Placebo Dose 1 N[a]=56 n[b] (%) | COMIRNATY Dose 2 N[a]=60 n[b] (%) | Placebo Dose 2 N[a]=62 n[b] (%) |
|---|---|---|---|---|
| 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[e] | | | | |
| 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[e] | | | | |
| 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[e] | | | | |
| 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.
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 issuance of the EUA for COMIRNATY, participants were unblinded to offer placebo participants COMIRNATY. Unblinded participants originally randomized to COMIRNATY and placebo recipients administered COMIRNATY continued to be followed for unsolicited adverse events including serious adverse events, throughout the study [from Dose 1 of COMIRNATY through 1 month (all unsolicited adverse events) and 6 months (serious adverse events) after the last vaccination]. 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

**Commented [A19]: FDA comment**
Pfizer: Please add a subsection to provide a description of the safety evaluation for the original BNT162b2 recipients who have at least 6 months of follow up post dose 2, through blinded and unblinded time periods.

**Pfizer-BioNTech response**
The Sponsor accepts and has provided the requested text.

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 (COMIRNATY =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 COMIRNATY recipients and 2.4 per 100 person-years among placebo recipients. In a similar analysis, in participants 56 years of age and older (COMIRNATY =8931, placebo = 8895), serious adverse events were reported at an incidence rate of 4.9 per 100 person-years among COMIRNATY recipients and 4.6 per 100 person-years among placebo recipients who received at least 1 dose of COMIRNATY 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 COMIRNATY 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 COMIRNATY.

*Non-Serious Adverse Events*

Overall in Study 2 in which 12,995 participants 16 through 55 years of age received COMIRNATY 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 COMIRNATY 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 (COMIRNATY = 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 COMIRNATY 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 COMIRNATY 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 COMIRNATY 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.

From Dose 1 up to the participant unblinding date, reports of lymphadenopathy were imbalanced with notably more cases in the COMIRNATY group (87) versus the placebo group (8).

Throughout the placebo-controlled safety follow-up period to date, Bell's palsy (facial paralysis) was reported by 4 participants in the COMIRNATY 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

**Commented [A20]: FDA comment**
Pfizer: Please delete this sentence and revise this introduction to describe the variable exposure caused by the unblinding that occurred in a phased manner, to include the actual difference in duration of follow up between groups. We will then report the following events as frequencies n/N (%) rather than incidence rates, as revised below.

**Pfizer-BioNTech response**
The Sponsor is not in agreement with FDA request and the FDA proposed revisions to the SAE and AE paragraphs. Proportion is more appropriate to summarize adverse events over a specified period of time for all participants. In this study however, participants had differential follow-up time due to the phased manner for unblinding, with approximately 42% of subjects with <4 months of follow up and approximately 58% with >+4 months follow-up. Pfizer therefore proposes to report incidence rates for safety events accounting for the differential follow-up time as a more accurate statistical summary of the safety results.

**Commented [A21]: Pfizer BioNTech** accepts FDA addition of the statement "From Dose 1 up to the participant unblinding date, reports of lymphadenopathy were imbalanced with notably more cases in the COMIRNATY group (87) versus the placebo group (8)"

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 COMIRNATY.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-marketing use of COMIRNATY, including under Emergency Use Authorization. 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.

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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 COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on four occasions, twice prior to mating and twice during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine *(see Animal Data)*.

Data

*Animal Data*

In a 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 COMIRNATY 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 COMIRNATY is excreted in human milk. Data are not available to assess the effects of COMIRNATY 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 COMIRNATY and any

**Commented [A22]: FDA comment**
Pfizer,
This subsection should focus on adverse reactions not observed in clinical trials. Please provide a rationale for inclusion of diarrhea, vomiting and pain in extremity (arm).

**Pfizer-BioNTech response**
The Sponsor identified Diarrhea, Vomiting and Pain in extremity (arm) as adverse reactions caused by the vaccine in the post-authorization setting, not the clinical study setting. In the clinical study, there was not differentiation in the frequency of these events between the placebo vs vaccine groups. Please refer to the Clinical Overview submitted with this response for a complete justification of these terms.

**Commented [A23]: FDA comment**
Pfizer,
Please add the PTs for "Dizziness" and "Dyspnea" and their corresponding SOCs to section 6.2

**Pfizer-BioNTech response**
The Sponsor is not in agreement with the FDA request. The Sponsor does not consider Dizziness and Dyspnea as adverse reactions independent of potential symptoms of a Vaccination stress-related response due to the vaccination process.

**Commented [A24]: FDA comment**
Pfizer,
Please include information regarding Pregnancy Exposure Registry for COM RNATY to monitor pregnancy outcomes in women exposed to COM RNATY during pregnancy. Please list the telephone number for the health care providers to call and register women who receive COM RNATY during pregnancy.

**Pfizer-BioNTech response**
The Sponsor is not in agreement with the inclusion of the Pregnancy Exposure Registry. The study registry is performed by the University of California San Diego (UCSD) with a limited enrollment of vaccinated pregnant women with COMIRNATY. The recruitment is handled by UCSD using their established registry procedures.

**Commented [A25]: Pfizer-BioNTech** accepts deletion of "reproductive and" from this sentence.

**Commented [A26]: Pfizer-BioNTech** accepts deletion of "reproductive and" from this sentence.

potential adverse effects on the breastfed child from COMIRNATY 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

Safety and effectiveness of COMIRNATY in individuals 16 through 17 years of age is based on safety and effectiveness data in this age group and in adults *[see Adverse Reactions (6) and Clinical Studies (14.1)]*.

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

### 8.5 Geriatric Use

Of the total number of COMIRNATY 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)]*. No overall differences in safety or effectiveness were observed between these recipients and younger recipients.

## 11 DESCRIPTION

Commented [A27]: Pfizer-BioNTech accepts FDA editorial revisions to this section.

COMIRNATY (COVID-19 Vaccine, mRNA) is a sterile suspension for injection for intramuscular use. COMIRNATY 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 COMIRNATY contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the COMIRNATY 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 glycol2000)-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.

COMIRNATY does not contain preservative.

The vial stoppers are not made with natural rubber latex.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA 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

COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a developmental toxicity study in rats with COMIRNATY~~,~~ ~~t~~There were no vaccine-related effects on female fertility *[see Use in Special Populations (8.1)]*.

## 14 CLINICAL STUDIES

Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, 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 Study 2, based on data accrued through March 13, 2021, approximately 44,000 participants 16 years of age and older were randomized equally and received 2 doses of COMIRNATY or placebo. 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 COMIRNATY 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.~~ Overall, among the total participants who received COMIRNATY or placebo, 51.4% or 50.5% were male and 48.6% or 49.5% were female, 4.8% or 4.6% were 12 through 15 years of age, 75.1% or 75.1% were 16 through 64 years of age, 20.1% or 20.3% were 65 years of age and older, 16.1% or 16.3% were 65 through 74 years of age, 4.0% or 4.0% ≥75 years of age and older, 82.9% or 83.1% were White, 8.5% or 8.6% were Black or African American, 0.9% or 0.9% were American Indian or Alaska Native, 4.6% or 4.5% were Asian, 0.3% or 0.1% Native Hawaiian or other Pacific Islander, 24.9% or 24.6% were Hispanic/Latino, 74.6% or 74.8% were non-Hispanic/Latino, 0.5% or 0.5% did not report ethnicity, 44.6% or 44.4% had comorbidities [participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least one of the Charlson comorbidity index category or body mass index (BMI) ≥30 kg/$m^2$ (16 years of age and older) or BMI ≥$95^{th}$ percentile (12 through 15 years of age)], respectively. The mean age at vaccination was 48.3 or 48.2 years and median age was 50.0 or 50.0 in participants who received COMIRNATY or placebo, respectively.

**Commented [A28]:** Pfizer-BioNTech accepts deletion of "and reproductive" from this sentence.

**Commented [A29]:** Pfizer BioNTech agrees with FDA deletion of the following statement "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." as well as the other edits within this paragraph.

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

| | ~~COMIRNATY (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)~~

**Commented [A30]:** FDA Comment
Pfizer: Please delete this table and describe demographics of the efficacy population using the March 2021 data cutoff, to also include percentages of the participants in the age group ≥65 years, and those with comorbidities (with a definition).

**Pfizer-BioNTech response**
Pfizer-BioNTech has updated the label as per FDA request.

Efficacy Against COVID-19

The population in the protocol pre-specified 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 [A31]:** Pfizer BioNTech agrees with FDA addition of this information.

The vaccine efficacy information is presented in Table ~~8~~5.

**Table ~~5~~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 | COMIRNATY N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d]) | Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d]) | Vaccine Efficacy % (95% CI) |
| All participants[e] | 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 | COMIRNATY N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d]) | Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d]) | Vaccine Efficacy % (95% CI) |
| All participants[e] | 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 [A32]:** FDA comment
Pfizer: Please describe the primary efficacy analysis in text as outlined below and remove Table 8.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COV D-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COV D-19 cases in the placebo group. The 95% credible interval for the vaccine efficacy was 90 3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

**Pfizer-BioNTech response**
The Sponsor proposes to retain the information as presented in the table as it is more informative and clearer for the healthcare provider.

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

The population for the updated vaccine efficacy analysis included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021~~0~~, representing up to 6 months of follow-up after Dose 2. Overall, 59.2% of participants in the COMIRNATY group and 57.3% of participants in the placebo group had ≥4 months of follow-up time after Dose 2 in the blinded placebo-controlled follow-up period.
~~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~~6.

**Table ~~9~~6: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants 16 Years of Age and Older 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 | COMIRNATY N[a]=~~20,998~~19,993 Cases n1[b] Surveillance Time[c] (n2[d]) | Placebo N[a]=~~21,096~~20,118 Cases n1[b] Surveillance Time[c] (n2[d]) | Vaccine Efficacy % (95% CI[e]) |
| All participants[f] | 77<br>~~6.247 (20,712)~~6.092 (19,711) | ~~850~~833<br>~~6.003 (20,713)~~5.857 (19,741) | ~~91.3~~91.1<br>~~(89.0, 93.2)~~(88.8, 93.1) |
| 16 through 64 years | 70<br>4.859 (15,519) | ~~710~~709<br>~~4.654 (15,515)~~4.654 (15,515) | ~~90.6~~90.5<br>~~(87.9, 92.7)~~(87.9, 92.7) |
| 65 years and older | 7<br>1.233 (4192) | 124<br>1.202 (4226) | 94.5<br>(88.3, 97.8) |
| ~~65 through 74 years~~ | ~~6~~<br>~~0.994 (3350)~~ | ~~98~~<br>~~0.966 (3379)~~ | ~~94.1~~<br>~~(86.6, 97.9)~~ |
| ~~75 years and older~~ | ~~1~~<br>~~0.239 (842)~~ | ~~26~~<br>~~0.237 (847)~~ | ~~96.2~~<br>~~(76.9, 99.9)~~ |

**Commented [A33]:** FDA comment
Pfizer: Please insert a sentence describing the percentage of participants with blinded placebo-controlled follow up ≥4months, to mirror the description of the Safety population.

**Pfizer-BioNTech response**
Pfizer-BioNTech has updated the label as per FDA request.

**Commented [A34]:** FDA comment
Pfizer: Please revise Updated VE tables to display VE for participants 16 years of age and older (exclude participants 12-15 years of age) for only confirmed cases that we agree upon (exclude participant 10031167 from all analyses, as previously communicated).

Please also delete the last 2 rows of each portion of the table: 65 through 74 years and 75 years and older.

**Pfizer-BioNTech response**
Pfizer has updated the table as per FDA request.
Source: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period– Subjects ≥16 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2– Evaluable Efficacy (7 Days) Population

**Commented [A35]:** Pfizer BioNTech accepts deletion of the 65 through 74 years and 75 years and older rows.

| First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection | | | |
|---|---|---|---|
| Subgroup | COMIRNATY<br>N[a]=~~22,166~~21,047<br>Cases<br>n1[b]<br>Surveillance Time[c] (n2[d]) | Placebo<br>N[a]=~~22,320~~21,210<br>Cases<br>n1[b]<br>Surveillance Time[c] (n2[d]) | Vaccine Efficacy %<br>(95% CI[e]) |
| All participants[f] | 81<br>~~6.509 (21,642)~~6.340 (20,533) | ~~873~~854<br>~~6.274 (21,689)~~6.110 (20,595) | ~~91.1~~90.9<br>~~(88.8, 93.0)~~(88.5, 92.8) |
| 16 through 64 years | 74<br>5.073 (16,218) | ~~727~~726<br>~~4.879 (16,269)~~4.879 (16,269) | 90.2<br>~~(87.6, 92.4)~~(87.5, 92.4) |
| 65 years and older | 7<br>1.267 (4315) | 128<br>1.232 (4326) | 94.7<br>(88.7, 97.9) |
| ~~65 through 74 years~~ | ~~6~~<br>~~1.021 (3450)~~ | ~~102~~<br>~~0.992 (3468)~~ | ~~94.3~~<br>~~(87.1, 98.0)~~ |
| ~~75 years and older~~ | ~~1~~<br>~~0.246 (865)~~ | ~~26~~<br>~~0.240 (858)~~ | ~~96.2~~<br>~~(77.2, 99.9)~~ |

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 COMIRNATY 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).~~

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, geographies, and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

~~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**~~

**Commented [A36]:** Pfizer BioNTech accepts deletion of the 65 through 74 years and 75 years and older rows.

**Commented [A37]:** FDA comment
Pfizer: This footnote should be removed based on our comment above to exclude all participants 12-15 years of age from this analysis.

Pfizer-BioNTech
The Sponsor accepts and has deleted the footnote.

**Commented [A38]:** FDA comment
Pfizer: Please delete Table 10-13.

Pfizer-BioNTech
The Sponsor accepts and has deleted Tables 10-13 and proposes a summary statement of the vaccine efficacy.

| Subgroup | COMIRNATY 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<br>3.246 (10,637) | 399<br>3.047 (10,433) | 90.1<br>(86.4, 93.0) |
| Female | 35<br>3.001 (10,075) | 451<br>2.956 (10,280) | 92.4<br>(89.2, 94.7) |
| Ethnicity | | | |
| Hispanic or Latino | 29<br>1.786 (5161) | 241<br>1.711 (5120) | 88.5<br>(83.0, 92.4) |
| Not Hispanic or Latino | 47<br>4.429 (15,449) | 609<br>4.259 (15,484) | 92.6<br>(90.0, 94.6) |
| Race | | | |
| Black or African American | 4<br>0.545 (1737) | 48<br>0.527 (1737) | 91.9<br>(78.0, 97.9) |
| White | 67<br>5.208 (17,186) | 747<br>5.026 (17,256) | 91.3<br>(88.9, 93.4) |
| All others[f] | 6<br>0.494 (1789) | 55<br>0.451 (1720) | 90.0<br>(76.9, 96.5) |
| Country | | | |
| Argentina | 15<br>1.012 (2600) | 108<br>0.986 (2586) | 86.5<br>(76.7, 92.7) |
| Brazil | 12<br>0.406 (1311) | 80<br>0.374 (1293) | 86.2<br>(74.5, 93.1) |
| Germany | 0<br>0.047 (236) | 1<br>0.048 (242) | 100.0<br>(-3874.2, 100.0) |
| South Africa | 0<br>0.080 (291) | 9<br>0.074 (276) | 100.0<br>(53.5, 100.0) |
| Turkey | 0<br>0.027 (228) | 5<br>0.025 (222) | 100.0<br>(-0.1, 100.0) |
| United States | 50<br>4.674 (16,046) | 647<br>4.497 (16,094) | 92.6<br>(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 COMIRNATY 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**

| Subgroup | COMIRNATY 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<br>3.376 (11,103) | 411<br>3.181 (10,920) | 89.9<br>(86.2, 92.8) |
| Female | 37<br>3.133 (10,539) | 462<br>3.093 (10,769) | 92.1<br>(88.9, 94.5) |
| Ethnicity | | | |
| Hispanic or Latino | 32<br>1.862 (5408) | 245<br>1.794 (5391) | 87.4<br>(81.8, 91.6) |
| Not Hispanic or Latino | 48<br>4.615 (16,128) | 628<br>4.445 (16,186) | 92.6<br>(90.1, 94.6) |
| Race | | | |
| Black or African American | 4<br>0.611 (1958) | 49<br>0.601 (1985) | 92.0<br>(78.1, 97.9) |
| White | 69<br>5.379 (17,801) | 768<br>5.191 (17,880) | 91.3<br>(88.9, 93.3) |
| All others[f] | 8<br>0.519 (1883) | 56<br>0.481 (1824) | 86.8<br>(72.1, 94.5) |
| Country | | | |
| Argentina | 16<br>1.033 (2655) | 110<br>1.017 (2670) | 85.7<br>(75.7, 92.1) |
| Brazil | 14<br>0.441 (1419) | 82<br>0.408 (1401) | 84.2<br>(71.9, 91.7) |
| Germany | 0<br>0.047 (237) | 1<br>0.048 (243) | 100.0<br>(-3868.6, 100.0) |
| South Africa | 0<br>0.099 (358) | 10<br>0.096 (358) | 100.0<br>(56.6, 100.0) |
| Turkey | 0<br>0.029 (238) | 6<br>0.026 (232) | 100.0<br>(22.2, 100.0) |
| United States | 51<br>4.861 (16,735) | 664<br>4.678 (16,785) | 92.6<br>(90.2, 94.6) |

| Subgroup | COMIRNATY 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] |
|---|---|---|---|

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 COMIRNATY 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 | COMIRNATY 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<br>6.247 (20,712) | 850<br>6.003 (20,713) | 91.3<br>(89.0, 93.2) |
| At risk[g] | | | |
| Yes | 35<br>2.797 (9167) | 401<br>2.681 (9136) | 91.6<br>(88.2, 94.3) |
| No | 42<br>3.450 (11,545) | 449<br>3.322 (11,577) | 91.0<br>(87.6, 93.6) |
| Age group (years) and risk status | | | |
| 16 through 64 and not at risk | 41<br>2.776 (8887) | 385<br>2.661 (8886) | 89.8<br>(85.9, 92.8) |
| 16 through 64 and at risk | 29<br>2.083 (6632) | 325<br>1.993 (6629) | 91.5<br>(87.5, 94.4) |
| 65 and older and not at risk | 1<br>0.553 (1870) | 53<br>0.546 (1922) | 98.1<br>(89.2, 100.0) |
| 65 and older and at risk | 6<br>0.680 (2322) | 71<br>0.656 (2304) | 91.8<br>(81.4, 97.1) |
| Obese[h] | | | |

| Subgroup | COMIRNATY Na=20,998 Cases n1b Surveillance Timec (n2d) | Placebo Na=21,096 Cases n1b Surveillance Timec (n2d) | Vaccine Efficacy % (95% CI)e |
|---|---|---|---|
| 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 COMIRNATY group; 16 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 ≥95$^{th}$ 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 95$^{th}$ 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**

| Subgroup | COMIRNATY Na=22,166 Cases n1b Surveillance Timec (n2d) | Placebo Na=22,320 Cases n1b Surveillance Timec (n2d) | Vaccine Efficacy % (95% CI)e |
|---|---|---|---|
| First COVID-19 occurrence from 7 days after Dose 2f | 81 6.509 (21,642) | 873 6.274 (21,689) | 91.1 (88.8, 93.0) |
| At riskg: | | | |
| 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) |

**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 | COMIRNATY 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] |
|---|---|---|---|
| Age group (years) and risk status | | | |
| 16 through 64 and not at risk | 44<br>2.887 (9254) | 397<br>2.779 (9289) | 89.3<br>(85.4, 92.4) |
| 16 through 64 and at risk | 30<br>2.186 (6964) | 330<br>2.100 (6980) | 91.3<br>(87.3, 94.2) |
| 65 and older and not at risk | 1<br>0.566 (1920) | 55<br>0.559 (1966) | 98.2<br>(89.6, 100.0) |
| 65 and older and at risk | 6<br>0.701 (2395) | 73<br>0.672 (2360) | 92.1<br>(82.0, 97.2) |
| Obese[h] | | | |
| Yes | 28<br>2.207 (7139) | 319<br>2.158 (7235) | 91.4<br>(87.4, 94.4) |
| No | 53<br>4.301 (14,497) | 554<br>4.114 (14,448) | 90.8<br>(87.9, 93.2) |
| Age group (years) and obesity status | | | |
| 16 through 64 and not obese | 49<br>3.303 (10,629) | 458<br>3.158 (10,614) | 89.8<br>(86.2, 92.5) |
| 16 through 64 and obese | 25<br>1.768 (5584) | 269<br>1.719 (5649) | 91.0<br>(86.4, 94.3) |
| 65 and older and not obese | 4<br>0.850 (2899) | 82<br>0.811 (2864) | 95.3<br>(87.6, 98.8) |
| 65 and older and obese | 3<br>0.417 (1415) | 46<br>0.420 (1462) | 93.4<br>(79.5, 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 COMIRNATY 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/m² or BMI ≥95$^{th}$ percentile [12 through 15 years of age]).

h Obese is defined as BMI ≥30 kg/m². For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95$^{th}$ percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy Against Severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of COMIRNATY 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~~7) 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 COMIRNATY and placebo groups.

**Table ~~14~~7: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older ~~and~~ With or Without* Prior SARS-CoV-2 Infection Based on Protocol† or Centers for Disease Control and Prevention (CDC)‡ Definition ~~After Dose 1 or~~ From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population ~~in~~ During the Placebo-Controlled Follow-up**

| Vaccine Efficacy – First Severe COVID-19 Occurrence | | | |
|---|---|---|---|
| | COMIRNATY Cases n1[a] Surveillance Time[b] (n2[cb]) | Placebo Cases n1[a] Surveillance Time[b] (n2[cb]) | Vaccine Efficacy % (95% CI[de]) |
| ~~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[fd] | 1 ~~6,522[ee] (21,649)~~6,353 (20,540) | 21 ~~6,404[ee] (21,730)~~6,237 (20,629) | 95.3 (70.9, 99.9) |
| **Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition** | | | |
| | COMIRNATY Cases n1[a] Surveillance Time[b] (n2[cb]) | Placebo Cases n1[a] Surveillance Time[b] (n2[cb]) | Vaccine Efficacy % (95% CI[de]) |
| ~~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[fd] | 0 ~~6,514[ee] (21,620)~~6,345 (20,513) | ~~32~~31 ~~6,391[ee] (21,693)~~6,225 (20,593) | 100 ~~(88.0, 100.0)~~(87.6, 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

† Severe illness from COVID-19 is defined in the protocol as 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

**Commented [A39]:** FDA comment
Pfizer: Please revise this table as follows:
1.Remove the rows for severe cases after Dose 1
2.Remove the specification of the FDA Definition of Severe Disease, as revised.

**Pfizer-BioNTech response**
The Sponsor accepts the FDA requests. The original table presented results for all participants 12 years of age or older. To be consistent with other updated VE analyses in the label, e.g. Table 6, 7 days after Dose 2 results were updated for participants 16 years of age or older. Pfizer BioNTech also proposes to add population to table title and rearranged footnote to be consistent with Table 6.

**Commented [A40]:** Pfizer BioNTech accepts the replacement of "FDA" with "Protocol" in the table title and footnotes.

**Commented [A41]:** Source: Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2– Blinded Placebo-Controlled Follow-up Period– Subjects ≥16 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2– Evaluable Efficacy (7 Days) Population

**Commented [A42]:** Source: Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2– Blinded Placebo-Controlled Follow-up Period – Subjects ≥16 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2– Evaluable Efficacy (7 Days) Population

[1] 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 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

c n2 = Number of participants at risk for the endpoint

de 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~~

~~fd 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~~

~~ge 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

COMIRNATY 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 provided but shipped separately, and should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as a 10 mL single-use vial manufactured by Hospira, Inc (NDC 0409-4888-10), or a 2 mL single-use vial manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02).

**Commented [A43]: FDA comment**
Pfizer,
Please include a description of the vials from each of the two suppliers and include NDC numbers for cartons and containers of diluent from each of the manufacturers.

**Pfizer-BioNTech response**
Pfizer-BioNTech has updated the label as per FDA request.

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.

Frozen Vials Prior to Use

Cartons of COMIRNATY 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.

If an ultra-low temperature freezer is not available, the thermal container in which COMIRNATY 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 of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

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 -80°C to -60°C (-112°F to -76°F).

Thawed Vials Before Dilution

*Thawed Under Refrigeration*

Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 1 month. 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 25°C (77°F)] 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.

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.

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.

## 17 PATIENT COUNSELING INFORMATION

Inform vaccine recipient of the potential benefits and risks of vaccination with COMIRNATY.

Inform vaccine recipient of the importance of completing the two dose vaccination series.

~~There is a pregnancy exposure registry for COMIRNATY. Encourage individuals exposed to COMIRNATY around the time of conception or during pregnancy to register by calling …..~~

Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers hhs.gov.

**Commented [A44]: Pfizer-BioNTech comment**
The Sponsor is not in agreement with the inclusion of the Pregnancy Exposure Registry. The study registry is performed by the USD with a limited enrollment of vaccinated pregnant women with COM RNATY. The recruitment will be handled by the UCSD procedures.

**Commented [A45]: FDA comment**
Pfizer,
We do not concur; please delete.

**Pfizer-BioNTech response**
The Sponsor accepts deletion of the website and telephone number for general questions.

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

Commented [A46]: Pfizer BioNTech proposes to update the website link.

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.~~2~~3

US Govt. License No. x

CPT Code x

Commented [A47]: FDA comment
Pfizer,
CPT codes are not typically included in labeling. Please provide a rationale for inclusion.

Pfizer-BioNTech response
The Sponsor proposes to retain the CPT code in the label for consistency with other Pfizer Vaccine label such as Trumenba and Prevnar 13.