

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TRADENAME/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: YYY Y

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

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 reports of adverse events suggest increased risks of myocarditis and pericarditis, particularly 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 years of age and older, the most commonly reported adverse reactions (>10%) were pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, fever, and injection site swelling (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: M/YYYY

Commented [A1]: Pfizer-BioNTech comment

The Sponsor has revised the placeholder "TRADENAME" to the FDA approved "COMIRNATY" tradename through the USPI. Only the first instance of this revision is shown in tracked mode.

Commented [A2]: FDA comment

Pfizer: we have inserted a place holder W/P for myocarditis/pericarditis based on the fact sheet language. We anticipate that this will be further revised.

Pfizer-BioNTech response

The Sponsor accepts the FDA proposed text and acknowledges the FDA comment.

Commented [A3]: FDA comment

Pfizer: Please provide percentages for each adverse reaction—i.e., " were pain at the injection site (X%), fatigue (X%) broken out by age (16 through 55 yrs and 56 and older), "

Pfizer-BioNTech response

The Sponsor has not revised this text in the Highlights section as the requested information is not captured in the Full Prescribing Information (FPI). The FDA requested information is more appropriate for inclusion in the FPI vs the Highlights page. The Sponsor will review the Highlights page once the section 6 is further reviewed by FDA.

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

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


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 0.9% Sodium Chloride Injection, USP (provided but shipped separately) to form COMIRNATY. Do not add more than 1.8 mL of diluent.
- **ONLY** use 0.9% Sodium Chloride Injection, USP as the diluent.
- After dilution, 1 vial contains 6 doses of 0.3 mL.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
 <p>No more than 2 hours at room temperature (up to 25 °C / 77 °F)</p>	<ul style="list-style-type: none">• Thaw vial(s) of COMIRNATY before use either by:<ul style="list-style-type: none">○ 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 5 days 1 month.○ Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.• Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

Commented [A4]: FDA comment

Pfizer: based on information in the BLA the saline diluent will be provided separately from the vials of vaccine. We have revised the text since the diluent is provided separately.

Pfizer-BioNTech response

The Sponsor is not in agreement to revise the text to specify only the provided sodium chloride can be used to dilute the vaccine. The Sponsor will be providing the sodium chloride separately but if an alternate brand of sodium chloride is used, there is no impact to product quality.

Pfizer-BioNTech proposed revision

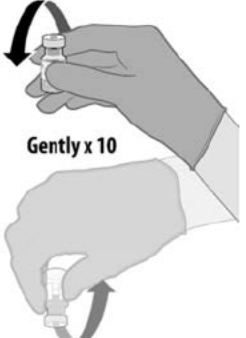
ONLY use **the provided** 0.9% Sodium Chloride Injection, USP as the diluent.

Commented [A5]: FDA comment

Pfizer: the storage time in the fact sheets is one month. Please explain why this is 5 days.

Pfizer-BioNTech response

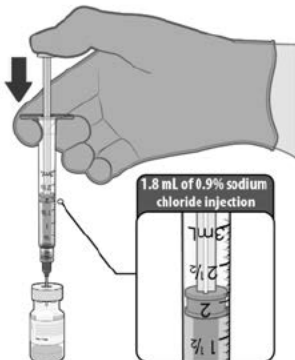
The information has been revised to reflect "1 month" as aligned with the EUA Fact Sheet. The draft USPI was provided to FDA for review prior to the FDA approval of the revised 1-month storage time. The text has now been updated to reflect the "1 month" information.



Gently x 10

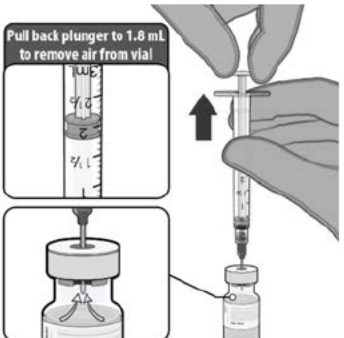
- Before dilution invert vaccine vial gently 10 times.
- Do not shake.
- Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles.
- Do not use if liquid is discolored or if other particles are observed.

DILUTION



1.8 mL of 0.9% sodium chloride injection

- ~~Obtain-Obtain~~ sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.



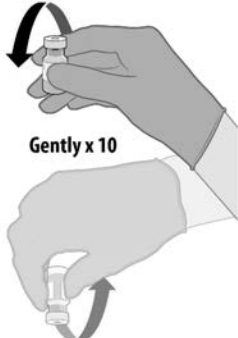

Pull back plunger to 1.8 mL to remove air from vial

- Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.

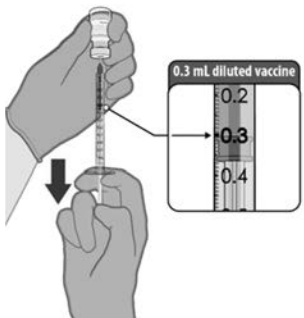
Commented [A6]: Pfizer-BioNTech response
 The Sponsor is not in agreement to revise the text to specify only the provided sodium chloride can be used to dilute the vaccine. The Sponsor will be providing the sodium chloride separately but if an alternate brand of sodium chloride is used, there is no impact to product quality.

Pfizer-BioNTech proposed revision

- ~~Obtain-Obtain~~ **Use the provided** sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.

 <p>Gently x 10</p>	<ul style="list-style-type: none"> • Gently invert the vial containing the COMIRNATY 10 times to mix. • <u>Do not shake.</u> • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	<ul style="list-style-type: none"> • Record the date and time of dilution on the COMIRNATY vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY

	<ul style="list-style-type: none"> • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw <u>0.3 mL</u> of COMIRNATY preferentially using low dead-volume syringes and/or needles. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Administer immediately.
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2.2 Administration Information

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.

Administer COMIRNATY intramuscularly.

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

Reports of adverse events following use of COMIRNATY under EUA suggest increased risks of myocarditis and pericarditis, particularly following the second dose. Typically, onset of symptoms has been within a few days following receipt of COMIRNATY. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, but information is not yet available about potential long-term sequelae. The decision to administer COMIRNATY to an individual with a history of myocarditis or

Commented [A7]: FDA comment
Pfizer: We have inserted the text in the current fact sheet for vaccination providers as a placeholder but we expect that this will be further revised.

Text based on FS (changed "Pfizer-BioNTech COV D-19 Vaccine" to "TRADENAME")

Pfizer-BioNTech response
The Sponsor accepts the FDA proposed text and acknowledges the FDA comment.

pericarditis should take into account the individual's clinical circumstances. The CDC has published clinical considerations relevant to myocarditis and pericarditis associated with administration of COMIRNATY (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

~~5.2 Concurrent Illness at Time of Vaccination~~

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

~~5.3 Concurrent Illness at Time of Vaccination~~

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

~~5.3.1 Syncope~~

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

~~5.3.2 Altered Immunocompetence~~

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

~~5.4 Bleeding Precautions~~

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

~~5.6 Bleeding Precautions~~

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

~~5.5.7 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, 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 (0.9%), 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.~~

~~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%).~~

Commented [A8]: Pfizer-BioNTech comment
The Sponsor is not in agreement with the deletion of this information as this is important information for the healthcare provider.

Commented [A9]: Pfizer-BioNTech comment
The Sponsor is not in agreement with the deletion of this information as this is important information for the healthcare provider.

[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.](#)

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

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

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

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

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days following each dose of COMIRNATY and placebo in the subset of participants

Commented [A10]: Pfizer-BioNTech response
The Sponsor is not in agreement with the deletion of this information. The Sponsor proposes to retain this information as the deletion will have adverse reactions that are below the 10% threshold to be removed from the USPI.

Please refer to the Sponsor response in the Highlights page.

Commented [A11]: FDA comment
Pfizer: We have included a couple of very high level comments in this section of the PI. Additional comments will be provided after review of this section.

Pfizer-BioNTech response
The Sponsor acknowledges the FDA's comment.

Commented [A12]: FDA comment
Pfizer: Please revise text to clarify that Study 1 was conducted in Germany and that Study 2 was conducted in the United States, Argentina, Brazil, Turkey, South Africa, and Germany.

Pfizer-BioNTech response
The Sponsor accepts and has revised the text.

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 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.

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

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)
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^e				
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^e				
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)

	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 (%)
Use of antipyretic or pain medication ^f	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

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

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

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

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

b n = Number of participants with the specified reaction

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

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

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

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

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

	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

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
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)

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

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

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

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

b n = Number of participants with the specified reaction

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

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

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

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

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

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

	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^c				
Any (>2.0 cm)	2 (3.7)	3 (5.4)	4 (6.7)	1 (1.6)
Mild	2 (3.7)	1 (1.8)	3 (5.0)	1 (1.6)
Moderate	0	0	1 (1.7)	0
Severe	0	2 (3.6)	0	0
Swelling^c				
Any (>2.0 cm)	3 (5.6)	1 (1.8)	5 (8.3)	0
Mild	2 (3.7)	0	2 (3.3)	0
Moderate	1 (1.9)	0	3 (5.0)	0
Severe	0	1 (1.8)	0	0

	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^c				
Any	22 (40.7)	15 (26.8)	24 (40.0)	12 (19.4)
Mild	15 (27.8)	9 (16.1)	12 (20.0)	5 (8.1)
Moderate	7 (13.0)	5 (8.9)	9 (15.0)	7 (11.3)
Severe	0	1 (1.8)	3 (5.0)	0
Headache^c				
Any	11 (20.4)	18 (32.1)	18 (30.0)	12 (19.4)
Mild	7 (13.0)	10 (17.9)	8 (13.3)	8 (12.9)
Moderate	4 (7.4)	7 (12.5)	8 (13.3)	4 (6.5)
Severe	0	1 (1.8)	2 (3.3)	0
Chills^c				
Any	6 (11.1)	5 (8.9)	14 (23.3)	4 (6.5)
Mild	5 (9.3)	4 (7.1)	5 (8.3)	3 (4.8)
Moderate	1 (1.9)	1 (1.8)	8 (13.3)	1 (1.6)
Severe	0	0	1 (1.7)	0

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

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (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.

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 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 Post Marketing 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)

Gastrointestinal Disorders: diarrhea, vomiting

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

Commented [A13]: FDA comment

Pfizer- Please re-order list of systems alphabetically.

Pfizer-BioNTech response

The Sponsor accepts and has revised the list of systems alphabetically.

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 reproductive and 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 reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of 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.

Commented [A14]: Pfizer-BioNTech comment

The Sponsor accepts the FDA proposed revisions with modifications. The Sponsor proposes to include the text "reproductive" in describing the study to be consistent with the text in the *Animal Data* section.

Pfizer-BioNTech proposed revision

A reproductive and developmental toxicity study [.]. These studies revealed no evidence of harm to the fetus due to the vaccine (~~see~~ (*see Animal Data below*)).

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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 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.

Commented [A15]: Pfizer-BioNTech comment

The Sponsor accepts with FDA proposed text with a modification. The Sponsor proposes to use the term "individuals" for more precision.

Pfizer-BioNTech proposed revision

Safety and effectiveness of TRADENAME in adolescents 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)*].

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

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 glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

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 studies, a developmental and reproductive toxicity study in rats with COMIRNATY, there were no vaccine-related effects on female fertility [see *Use in Special Populations (8.1)*].

14 CLINICAL STUDIES

14.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or

Commented [A16]: Pfizer-BioNTech response

The Sponsor is not in agreement to revise the text to specify only the provided sodium chloride can be used to dilute the vaccine. The Sponsor will be providing the sodium chloride separately but if an alternate brand of sodium chloride is used, there is no impact to product quality.

Pfizer-BioNTech proposed revision

COMIRNATY is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of the provided sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine.

Commented [A17]: FDA comment

Pfizer: this was revised to be consistent with the NP name

Pfizer-BioNTech response

The Sponsor accepts.

Commented [A18]: FDA comment

Pfizer: Subsection 8.1 refers to a single study. Please clarify if "studies" should be revised to "a study."

Pfizer-BioNTech response

The text has been revised to reflect the single developmental and reproductive toxicity study.

Commented [A19]: FDA comment

Pfizer: We have not reviewed this section. Comments will be provided after review.

Pfizer-BioNTech response

The Sponsor acknowledges the FDA comment.

hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

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

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the 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.

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/m²)
- Diabetes (Type 1, Type 2, or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Efficacy Against COVID-19

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

The vaccine efficacy information is presented in Table 8.

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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	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	19	94.7

	0.530 (4044)	0.532 (4067)	(66.8, 99.9) ^g
	1	14	92.9
65 to 74 years	0.424 (3239)	0.423 (3255)	(53.2, 99.8) ^g
	0	5	100.0
75 years and older	0.106 (805)	0.109 (812)	(-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

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 $\theta = r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group

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

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

The updated vaccine efficacy information is presented in Table 9.

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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	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)
All participants ^f	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 through 64 years	70 4.859 (15,519)	710 4.654 (15,515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 through 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	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
All participants ^f	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

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)

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

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

Subgroup	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 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10,075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			

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
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others ^f	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

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

Included confirmed cases in participants 12 through 15 years of age: 0 in the 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 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others ^f	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

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

Included confirmed cases in participants 12 through 15 years of age: 0 in the 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 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk ^g			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese ^h			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

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

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

a N = Number of participants in the specified group

b n1 = Number of participants meeting the endpoint definition

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
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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/m² or BMI $\geq 95^{\text{th}}$ percentile [12 through 15 years of age])

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

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

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
First COVID-19 occurrence from 7 days after Dose 2 ^f	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk ^g			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese ^h			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)

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
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

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 $\geq 95^{\text{th}}$ 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 95th 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) 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: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on FDA[†] or Centers for Disease Control and Prevention (CDC)[‡] Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

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

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

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

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

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

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen $\leq 93\%$ 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

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

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

a n1 = Number of participants meeting the endpoint definition

b n2 = Number of participants at risk for the endpoint

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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]. After dilution, 1 vial contains 6 doses of 0.3 mL.

Commented [A20]: FDA comment
Pfizer: Please include instructions on how to store the provided saline diluent.

Pfizer-BioNTech response
The Sponsor accepts and has included the storage information for the 0.9% Sodium Chloride Injection, USP diluent.

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 -80°C to -60°C (-112°F to -76°F) 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 -80°C to -60°C (-112°F to -76°F). 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 -90°C to -60°C (-130°F to -76°F). Storage within this temperature range 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 5 days (~~120 hours~~) 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.

Commented [A21]: FDA comment
Pfizer: This is not consistent with the FS which states "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." Please revise if necessary.

Pfizer-BioNTech response
The information has been revised to align with the EUA Fact Sheet. The draft USPI was provided to FDA for review prior to the FDA approval of the revised statement. The text has now been updated.

Commented [A22]: FDA comment
Pfizer: the storage time in the FS is "1 month". Please explain why this is 5 days.

Pfizer-BioNTech response
The information has been revised to reflect "1 month" to align with the EUA Fact Sheet. The draft USPI was provided to FDA for review prior to the FDA approval of the revised 1-month storage time. The information has now been updated to reflect the "1 month" information.

Transportation of Thawed Vials

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

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.

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.

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

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

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

<u>Website</u>	<u>Telephone number</u>
www.comirnatyhcp.com 	1-877-829-2619 (1-877-VAX-CO19)

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

Commented [A23]: FDA comment
Pfizer: This statement is not in the FS. See comments above regarding whether storage of undiluted vials at 2-8C is for 5days or one month.

Pfizer-BioNTech response
The text has been revised to align with the EUA Fact Sheet. The draft USPI was provided to FDA for review prior to the FDA approval of the deleted text.

Commented [A24]: Pfizer-BioNTech comment
The Sponsor proposes to retain the inclusion of website, QR code and telephone contact information as it may provide helpful and current information for the healthcare provider. Updated QR codes and website have been proposed and may be further revised.

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Manufactured by
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| LAB-1448-0.42

US Govt. License No. x

| ~~CPT Code~~ x ~~CPT Code~~ x

Commented [A25]: Pfizer-BioNTech comment
The Sponsor is not in agreement with the deletion of the placeholder information for the CPT Code.