

**FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE
(VACCINATION PROVIDERS)**

EMERGENCY USE AUTHORIZATION (EUA)

**PFIZER-BIONTECH COVID-19 VACCINE, BIVALENT
(ORIGINAL ANDOMICRON BA.4/BA.5)**

**BOOSTER DOSE FOR 12 YEARS OF AGE AND OLDER
DO NOT DILUTE**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for active immunization to prevent COVID-19 in individuals 12 years of age and older.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is hereafter referred to as Pfizer-BioNTech COVID-19 Vaccine, Bivalent. It is supplied in single dose and multiple dose vials with gray caps and labels with gray borders.

DO NOT DILUTE PRIOR TO USE.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in individuals 12 years of age and older as a single booster dose administered at least 2 months after either:

- completion of primary vaccination with any authorized or approved COVID-19 vaccine, or
- receipt of the most recent booster dose with any authorized or approved monovalent¹ COVID-19 vaccine.

This Fact Sheet pertains only to Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in a single dose and multiple dose vial with a gray cap and a label with a gray border, which **MUST NOT BE DILUTED PRIOR TO USE.**

Pfizer-BioNTech COVID-19 Vaccine, Bivalent, which is supplied in a single dose and multiple dose vial with a gray cap and a label with a gray border, should not be used in individuals 6 months through 11 years of age.²

² Different presentations of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are available. Pfizer-BioNTech COVID-19 Vaccine, Bivalent, supplied in multiple dose vials with maroon caps and labels with maroon borders, is available for use as a third dose of the primary series in individuals 6 months through 4 years of age. Pfizer-BioNTech COVID-19 Vaccine, Bivalent, supplied in multiple dose vials with orange caps and labels with orange borders is available for use as a single booster dose in individuals 5 through 11 years of age.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of myocarditis, cases of pericarditis, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine, Bivalent. See “MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE, BIVALENT ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION” for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is a suspension for intramuscular injection.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for active immunization to prevent COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

The storage, preparation, and administration information in this Fact Sheet apply to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in:

- single dose vials with gray caps and labels with gray borders, and
- multiple dose vials with gray caps and labels with gray borders.

DO NOT DILUTE PRIOR TO USE.

Storage and Handling

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

Do not refreeze thawed vials.

Vial Storage Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine, Bivalent may arrive frozen at ultra-cold conditions in thermal containers with dry ice.

Once received, frozen vials may be immediately transferred to the refrigerator [2°C to 8°C (35°F to 46°F)], thawed and stored for up to 10 weeks. The 10-week refrigerated expiry date should be recorded on the carton at the time of transfer. A carton of 10 single dose vials may take up to 2 hours to thaw at this temperature. A carton of 10 multiple dose vials may take up to 6 hours to thaw at this temperature.

Alternatively, frozen vials may be stored in an ultra-low temperature freezer at -90°C to -60°C (-130°F to -76°F) for up to 18 months from the date of manufacture. Do not store vials at -25°C to -15°C (-13°F to 5°F). Once vials are thawed, they should not be refrozen.

If cartons of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are received at 2°C to 8°C (35°F to 46°F), they should be stored at 2°C to 8°C (35°F to 46°F). Check that the carton has been updated to reflect the 10-week refrigerated expiry date.

Regardless of storage condition, the vaccine should not be used after 18 months from the date of manufacture printed on the vial and cartons.

Vial Storage During Use

If not previously thawed at 2°C to 8°C (35°F to 46°F), allow vials to thaw at room temperature [up to 25°C (77°F)] for 30 minutes.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be stored at room temperature [8°C to 25°C (46°F to 77°F)] for a total of 12 hours prior to the first puncture. After first puncture, the multiple dose vial should be held between 2°C to 25°C (35°F to 77°F). Multiple dose vials should be discarded 12 hours after first puncture.

Transportation of Vials

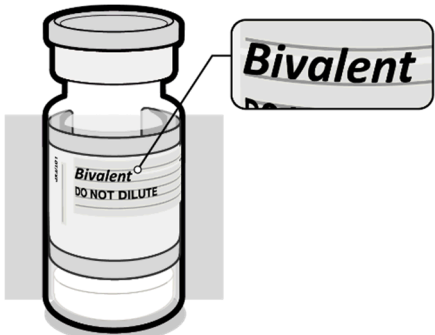
If local redistribution is needed, vials may be transported at -90°C to -60°C (-130°F to -76°F) or at 2°C to 8°C (35°F to 46°F).

Dosing and Schedule

A single booster dose (0.3 mL) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be administered at least 2 months after completion of primary vaccination with any authorized or approved COVID-19 vaccine or after receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.

Dose Preparation

- Pfizer-BioNTech COVID-19 Vaccine, Bivalent vials contain a frozen suspension without preservative. Each vial must be thawed prior to administration. **DO NOT DILUTE** prior to use.
- 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)].
- Refer to thawing and preparation instructions in the panels below.

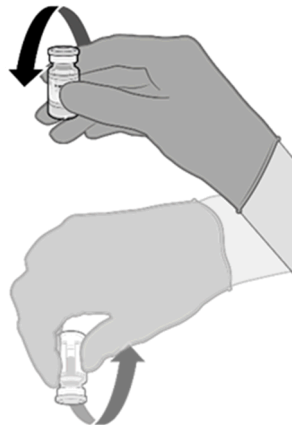
Preparation Instructions	
Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vial with Gray Cap and Label with Gray Border – VIAL VERIFICATION	
 <p>✓ Gray cap and label with gray border.</p>	<ul style="list-style-type: none">• Verify that the vial of Pfizer-BioNTech COVID-19 Vaccine, Bivalent:<ul style="list-style-type: none">○ has a gray cap and a label with a gray border○ states Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

THAWING PRIOR TO USE



Store in the refrigerator for up to 10 weeks prior to use.

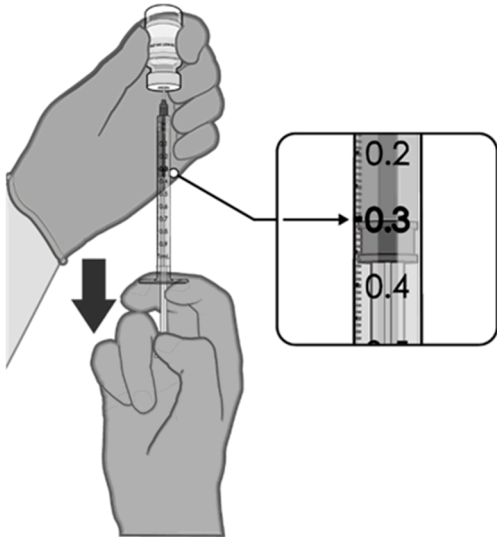
- Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent before use either by:
 - Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)].
 - A carton of 10 single dose vials may take up to 2 hours to thaw.
 - A carton of 10 multiple dose vials may take up to 6 hours to thaw.
 - Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.
- Thawed vials can be stored in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 10 weeks prior to use.
- Thawed vials may be stored at room temperature [up to 25°C (77°F)] for up to 12 hours prior to use.



Gently × 10

- Before use, mix by inverting vaccine vial gently 10 times.
- Do not shake.
- Prior to mixing, the thawed vaccine may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should appear as a white to off-white suspension with no visible particles.
- Do not use if liquid is discolored or if particles are observed after mixing.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES



Withdraw 0.3 mL dose of vaccine.

Single Dose Vial

- Withdraw a single 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.
- Administer immediately.
- Discard vial and any excess volume.

Multiple Dose Vial

- Multiple dose vials contain 6 doses of 0.3 mL each.
- Withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent preferentially using low dead-volume syringes and/or needles. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses from a single vial.
- Administer immediately.
- If the amount of vaccine remaining in a multiple dose vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

Multiple Dose Vial – Record Date and Time of First Puncture



**Record the date and time of first puncture.
Use within 12 hours after first puncture.**

- Record the date and time of first vial puncture on the Pfizer-BioNTech COVID-19 Vaccine, Bivalent multiple dose vial label.
- Store between 2°C to 25°C (35°F to 77°F).
- Discard any unused vaccine 12 hours after first puncture.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vaccine will be a white to off-white suspension. Do not administer if vaccine is discolored or contains particulate matter.

After withdrawing a single 0.3 mL dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent, administer immediately.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine, Bivalent to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (*see Full EUA Prescribing Information*).

Warnings

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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

Monitor Pfizer-BioNTech COVID-19 Vaccine, Bivalent recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

Myocarditis and Pericarditis

Postmarketing safety data with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

Postmarketing data with authorized or approved monovalent mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following receipt of the second primary series dose or first booster dose, with most booster doses likely administered at least 5 months after completing primary vaccination. For the Pfizer-BioNTech COVID-19 Vaccine, the observed risk is higher among adolescent males and adult males under 40 years of age than among females and older males, and the observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for

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

Syncope

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

Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

Limitation of Effectiveness

Pfizer-BioNTech COVID-19 Vaccine, Bivalent may not protect all vaccine recipients.

Adverse Reactions

The safety of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent is based on:

- safety data from a clinical study which evaluated a booster dose of Pfizer-BioNTech's bivalent COVID-19 vaccine (Original and Omicron BA.1), not authorized or approved, hereafter referred to as bivalent vaccine (Original and Omicron BA.1),
- safety data from clinical trials which evaluated primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, and
- post marketing safety data with Pfizer-BioNTech COVID-19 Vaccine.

The safety data accrued with the bivalent vaccine (Original and Omicron BA.1) and with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process. The bivalent vaccine (Original and Omicron BA.1) contained 15 mcg of nucleoside-modified messenger RNA (modRNA) encoding the S-glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 15 mcg of modRNA encoding the S-glycoprotein of SARS-CoV-2 Omicron variant lineage BA.1, for a total of 30 mcg modRNA per dose. This is the same total quantity of modRNA per dose as a dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent and as a dose of Pfizer-BioNTech COVID-19 Vaccine authorized for primary vaccination in individuals 12 years of age and older (and previously, but no longer, authorized for booster vaccination in individuals 12 years of age and older).

Adverse Reactions in Clinical Trials

Adverse reactions following administration of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine or the bivalent vaccine (Original and Omicron BA.1) that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, injection site swelling, fever, injection site redness, lymphadenopathy, nausea, malaise, pain in extremity, rash, and decreased appetite (*see Full EUA Prescribing Information*).

Adverse Reactions Identified in Post Authorization Experience

Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), diarrhea, vomiting, pain in extremity (arm), syncope, and dizziness have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

Myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

Additional adverse reactions, some of which may be serious, may become apparent with post-authorization use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the “Vaccine Information Fact Sheet for Recipients and Caregivers” (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Vaccine Information Fact Sheet for Recipients and Caregivers) prior to the individual receiving each dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent which is not an FDA-approved vaccine.
- There is an option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine, Bivalent.
- The significant known and potential risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE, BIVALENT ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION³

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, Bivalent the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine, Bivalent for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in individuals 12 years of age and older.
2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine, Bivalent or their caregiver, information consistent with the “Vaccine Information Fact Sheet for Recipients and Caregivers” prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine, Bivalent.
3. The vaccination provider must include vaccination information in the designated system.
4. The vaccination provider is responsible for mandatory reporting of the following as per your local system:
 - vaccine administration errors whether or not associated with an adverse event,
 - serious adverse events* (irrespective of attribution to vaccination),
 - cases of myocarditis,
 - cases of pericarditis,
 - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
 - cases of COVID-19 that result in hospitalization or death.
5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of myocarditis, cases of pericarditis, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine, Bivalent to recipients.

* Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;

³ Vaccination providers administering Pfizer-BioNTech COVID-19 Vaccine must adhere to the same reporting requirements.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent 1 of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING .

Vaccination providers may report other adverse events

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below.

Website	Email
www.pfizersafetyreporting.com	ARE.AEReporting@pfizer.com

ADDITIONAL INFORMATION

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

To access the most recent Pfizer-BioNTech COVID-19 Vaccine, Bivalent Fact Sheets, please scan the QR code provided below.

Global website
www.cvdvaccine.com 

AVAILABLE ALTERNATIVES

There may be clinical trials or availability under EUA of other COVID-19 vaccines -

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, Bivalent for active immunization to prevent COVID-19.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

For the authorized uses, although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at:
<https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.



Further information is available upon request
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END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

**FULL EMERGENCY USE
AUTHORIZATION (EUA) PRESCRIBING
INFORMATION**

**PFIZER-BIONTECH COVID-19 VACCINE,
BIVALENT (ORIGINAL ANDOMICRON
BA.4/BA.5)**

**FULL EMERGENCY USE AUTHORIZATION PRESCRIBING
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* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

This EUA Prescribing Information pertains only to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), hereafter referred to as Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

2 DOSAGE AND ADMINISTRATION

The storage, preparation, and administration information in this Prescribing Information apply to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in:

- single dose vials with gray caps and labels with gray borders, and
- multiple dose vials with gray caps and labels with gray borders.

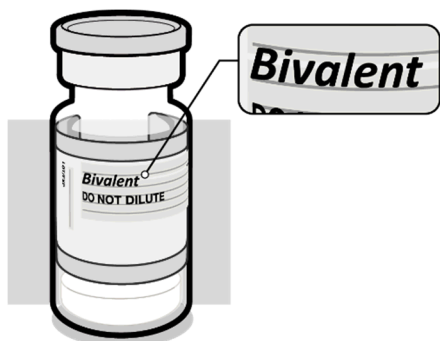
DO NOT DILUTE PRIOR TO USE.

2.1 Preparation for Administration

- Pfizer-BioNTech COVID-19 Vaccine, Bivalent vials contain a frozen suspension without preservative. Each vial must be thawed prior to administration. **DO NOT DILUTE** prior to use.
- 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 (19)*].
- Refer to thawing and preparation instructions in the panels below.

Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine, Bivalent Vial with Gray Cap and Label with Gray Border – VIAL VERIFICATION



✓ Gray cap and label with gray border.

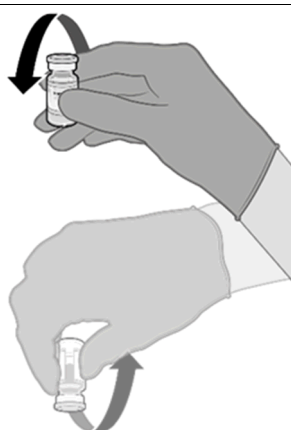
- Verify that the vial of Pfizer-BioNTech COVID-19 Vaccine, Bivalent:
 - has a gray cap and a label with a gray border
 - states Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

THAWING PRIOR TO USE



Store in the refrigerator for up to 10 weeks prior to use.

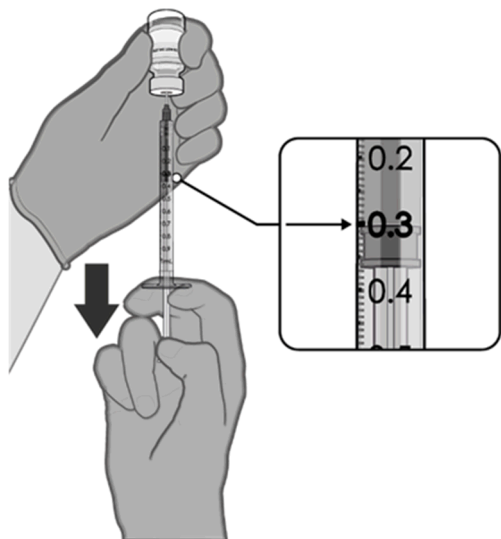
- Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent before use either by:
 - Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)].
 - A carton of 10 single dose vials may take up to 2 hours to thaw.
 - A carton of 10 multiple dose vials may take up to 6 hours to thaw.
 - Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.
- Thawed vials can be stored in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 10 weeks prior to use.
- Thawed vials may be stored at room temperature [up to 25°C (77°F)] for up to 12 hours prior to use.



Gently × 10

- Before use, mix by inverting vaccine vial gently 10 times.
- Do not shake.
- Prior to mixing, the thawed vaccine may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should appear as a white to off-white suspension with no visible particles.
- Do not use if liquid is discolored or if particles are observed after mixing.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES



Withdraw 0.3 mL dose of vaccine.

Single Dose Vial

- Withdraw a single 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.
- Administer immediately.
- Discard vial and any excess volume.

Multiple Dose Vial

- Multiple dose vials contain 6 doses of 0.3 mL each.
- Withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent preferentially using low dead-volume syringes and/or needles. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses from a single vial.
- Administer immediately.
- If the amount of vaccine remaining in a multiple dose vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.

Multiple Dose Vial – Record Date and Time of First Puncture



**Record the date and time of first puncture.
Use within 12 hours after first puncture.**

- Record the date and time of first vial puncture on the Pfizer-BioNTech COVID-19 Vaccine, Bivalent multiple dose vial label.
- Store between 2°C to 25°C (35°F to 77°F).
- Discard any unused vaccine 12 hours after first puncture.

2.2 Administration Information

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The vaccine will be a white to off-white suspension. Do not administer if vaccine is discolored or contains particulate matter.

After withdrawing a single 0.3 mL dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent, administer immediately.

2.3 Vaccination Schedule

A single booster dose (0.3 mL) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be administered at least 2 months after completion of primary vaccination with any authorized or approved COVID-19 vaccine or after receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine.

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine, Bivalent is a suspension for injection.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is 0.3 mL [*see Dosage and Administration (2.1)*].

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine, Bivalent to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent [*see Description (13)*].

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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

Monitor Pfizer-BioNTech COVID-19 Vaccine, Bivalent recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

5.2 Myocarditis and Pericarditis

Postmarketing safety data with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

Postmarketing data with authorized or approved monovalent mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following receipt of the second primary series dose or first booster dose, with most booster doses likely administered at least 5 months after completing primary vaccination. For the Pfizer-BioNTech COVID-19 Vaccine, the observed risk is higher among adolescent males and adult males under 40 years of age than among females and older males, and the observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including 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, in particular in adolescents. 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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

5.5 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report all vaccine administration errors, all serious adverse events, cases of myocarditis, cases of pericarditis, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.⁴

The safety of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent is based on:

- safety data from a clinical study which evaluated a booster dose of Pfizer-BioNTech's bivalent COVID-19 vaccine (Original and Omicron BA.1), not authorized or approved, hereafter referred to as bivalent vaccine (Original and Omicron BA.1),
- safety data from clinical trials which evaluated primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, and
- post marketing safety data with Pfizer-BioNTech COVID-19 Vaccine.

The safety data accrued with the bivalent vaccine (Original and Omicron BA.1) and with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process. The bivalent vaccine (Original and Omicron BA.1) contained 15 mcg of nucleoside-modified messenger RNA (modRNA) encoding the S-glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 15 mcg of modRNA encoding the S-glycoprotein of SARS-CoV-2 Omicron variant lineage BA.1, for a total of 30 mcg modRNA per dose. This is the same total quantity of modRNA per dose as a dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent and as a dose of Pfizer-BioNTech COVID-19 Vaccine authorized for primary vaccination in individuals 12 years of age and older (and previously, but no longer, authorized for booster vaccination in individuals 12 years of age and older).

The clinical study that evaluated a booster dose of the bivalent vaccine (Original and Omicron BA.1) included participants greater than 55 years of age. Adverse reactions following administration of the bivalent vaccine (Original and Omicron BA.1) as a second booster dose included pain at the injection site (58.1%), fatigue (49.2%), headache (33.6%), muscle pain (22.3%), chills (13.0%), joint pain (11.3%), injection site redness (7.0%), injection site swelling (6.6%), fever (5.0%), lymphadenopathy (0.3%), nausea (0.3%), and malaise (0.3%).

In a clinical study of participants 18 through 55 years of age, adverse reactions following administration of a first booster dose of Pfizer-BioNTech COVID-19 Vaccine were pain at the injection site (83.0%), fatigue

⁴ Vaccination providers administering Pfizer-BioNTech COVID-19 Vaccine must adhere to the same reporting requirements.

(63.7%), headache (48.4%), muscle pain (39.1%), chills (29.1%), joint pain (25.3%), lymphadenopathy (5.2%), nausea (0.7%), decreased appetite (0.3%), rash (0.3%), and pain in extremity (0.3%). Severe allergic reactions (including anaphylaxis), myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

6.1 Clinical Trials Experience

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

Overall 3,013 participants 6 months through 4 years of age and 3,109 participants 5 through 11 years of age in Study 3 (NCT04816643) and 22,851 participants 12 years of age and older in Study 1 (NCT04380701) and Study 2 (NCT04368728) have received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine during the Phase 2/3 blinded placebo-controlled follow-up period. In a subset of Study 4 (NCT04955626), 305 participants greater than 55 years of age received a second booster dose with the bivalent vaccine (Original and Omicron BA.1).

Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose

In Study 4, a total of 610 participants greater than 55 years of age previously vaccinated with a 2-dose primary series and 1 booster dose of Pfizer-BioNTech COVID-19 Vaccine went on to receive a second booster dose with either Pfizer-BioNTech COVID-19 Vaccine or the bivalent vaccine (Original and Omicron BA.1).

The 305 participants greater than 55 years who received a second booster dose with Pfizer-BioNTech COVID-19 received it 5.3 to 13.1 months after receiving the first booster dose and had a median follow-up time of 1.8 months up to a data cut-off date of May 16, 2022. Their median age was 66 years (range 56 through 87 years of age), 47.5% were male and 52.5% were female, 87.9% were White, 18.7% were Hispanic/Latino, 4.3% were Asian, and 6.2% were Black or African American.

The 305 participants greater than 55 years who received a second booster dose with the bivalent vaccine (Original and Omicron BA.1) received it 4.7 to 11.5 months after receiving the first booster dose and had a median follow-up time of 1.7 months up to a data cut-off date of May 16, 2022. Their median age was 67 years (range 56 through 85 years of age), 53.1% were male and 46.9% were female, 89.8% were White, 14.8% were Hispanic/Latino, 5.2% were Asian, and 4.3% were Black or African American.

Solicited Local and Systemic Adverse Reactions

Table 1 and Table 2 present the frequency and severity of reported solicited local reactions and systemic reactions, respectively, within 7 days of a second booster dose of Pfizer-BioNTech COVID-19 Vaccine or bivalent vaccine (Original and Omicron BA.1).

In participants who received the bivalent vaccine (Original and Omicron BA.1), the mean duration of injection site pain, redness, and swelling was 2.2 days (range 1 to 12 days), 2.9 days (range 1 to 10 days), and 1.9 days (range 1 to 4 days), respectively.

Table 1: Local Adverse Reactions, by Maximum Severity, Within 7 Days After a Second Booster Dose – Participants Greater Than 55 Years of Age – Safety Population

	Pfizer-BioNTech COVID-19 Vaccine N ^a =298 n ^b (%)	Bivalent Vaccine (Original and Omicron BA.1) N ^a =301 n ^b (%)
Redness^c		
Any (>2 cm)	19 (6.4)	21 (7.0)
Mild	12 (4.0)	13 (4.3)
Moderate	6 (2.0)	8 (2.7)
Severe	1 (0.3)	0
Swelling^c		
Any (>2 cm)	18 (6.0)	20 (6.6)
Mild	10 (3.4)	14 (4.7)
Moderate	8 (2.7)	6 (2.0)
Severe	0	0
Pain at the injection site^d		
Any	179 (60.1)	175 (58.1)
Mild	154 (51.7)	159 (52.8)
Moderate	24 (8.1)	15 (5.0)
Severe	1 (0.3)	1 (0.3)

Note: Adverse Reactions were collected in the electronic diary (e-diary) from day of vaccination (Day 1) through Day 7 after the study vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the study vaccination.

b. n = Number of participants with the specified adverse 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: Systemic Adverse Reactions, by Maximum Severity, Within 7 Days After the Second Booster Dose – Participants Greater Than 55 Years of Age – Safety Population

	Pfizer-BioNTech COVID-19 Vaccine N ^a =298 n ^b (%)	Bivalent Vaccine (Original and Omicron BA.1) N ^a =301 n ^b (%)
Fever		
≥38.0°C	11 (3.7)	15 (5.0)
≥38.0°C to 38.4°C	6 (2.0)	11 (3.7)
>38.4°C to 38.9°C	5 (1.7)	0
>38.9°C to 40.0°C	0	4 (1.3)
>40.0°C	0	0
Fatigue^c		
Any	135 (45.3)	148 (49.2)
Mild	70 (23.5)	88 (29.2)
Moderate	64 (21.5)	55 (18.3)
Severe	1 (0.3)	5 (1.7)
Headache^c		
Any	79 (26.5)	101 (33.6)
Mild	47 (15.8)	71 (23.6)
Moderate	31 (10.4)	29 (9.6)

	Pfizer-BioNTech COVID-19 Vaccine N ^a =298 n ^b (%)	Bivalent Vaccine (Original and Omicron BA.1) N ^a =301 n ^b (%)
Severe	1 (0.3)	1 (0.3)
Chills^c		
Any	49 (16.4)	39 (13.0)
Mild	32 (10.7)	25 (8.3)
Moderate	17 (5.7)	14 (4.7)
Severe	0	0
Vomiting^d		
Any	4 (1.3)	5 (1.7)
Mild	2 (0.7)	5 (1.7)
Moderate	2 (0.7)	0
Severe	0	0
Diarrhea^e		
Any	13 (4.4)	27 (9.0)
Mild	10 (3.4)	18 (6.0)
Moderate	3 (1.0)	5 (1.7)
Severe	0	4 (1.3)
New or worsened muscle pain^c		
Any	59 (19.8)	67 (22.3)
Mild	35 (11.7)	40 (13.3)
Moderate	24 (8.1)	27 (9.0)
Severe	0	0
New or worsened joint pain^c		
Any	27 (9.1)	34 (11.3)
Mild	16 (5.4)	23 (7.6)
Moderate	11 (3.7)	11 (3.7)
Severe	0	0
Use of antipyretic or pain medication^f	80 (26.8)	88 (29.2)

Note: Adverse reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from day of vaccination (Day 1) through Day 7 after the study vaccination.

- N = Number of participants reporting at least 1 yes or no response for the specified adverse reaction after the study vaccination.
- n = Number of participants with the specified adverse reaction.
- Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
- Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
- 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.
- Severity was not collected for use of antipyretic or pain medication.

Unsolicited Adverse Events

Overall, the participants who received a second booster dose with the bivalent vaccine (Original and Omicron BA.1) had a median follow-up time of 1.7 months (range 1.0 to 2.0 months) to the cut-off date (May 16, 2022).

In an analysis of all unsolicited adverse events reported following the second booster dose, through 1 month after the booster dose, those assessed as adverse reactions not already captured by solicited local and systemic reactions were lymphadenopathy (n = 1, 0.3%) for the Pfizer-BioNTech COVID-19 Vaccine and (n = 1, 0.3%)

for the bivalent vaccine (Original and Omicron BA.1), nausea (n = 1, 0.3%) for the Pfizer-BioNTech COVID-19 Vaccine and (n = 1, 0.3%) for the bivalent vaccine (Original and Omicron BA.1), and malaise (n = 0) for the Pfizer-BioNTech COVID-19 Vaccine and (n = 1, 0.3%) for the bivalent vaccine (Original and Omicron BA.1).

Serious Adverse Events

Serious adverse events up to 1 month after the second booster dose in ongoing follow up were reported by no Pfizer-BioNTech COVID-19 Vaccine recipients and by 1 bivalent vaccine (Original and Omicron BA.1) recipient (1 serious adverse event considered unrelated to the vaccine).

Pfizer-BioNTech COVID-19 Vaccine

Primary Series

The safety of the primary series Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) was evaluated in participants 12 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.

Study BNT162-01 (Study 1) was a Phase 1/2, 2-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. 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 43,448 participants [21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo] in Phase 2/3 are 16 years of age or older (including 138 and 145 participants 16 and 17 years of age in the vaccine and placebo groups, respectively) and 2,260 participants are 12 through 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively).

In Study 2, 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].

Participants 16 Years of Age and Older

At the time of the analysis of Study 2 for the EUA, 37,586 [18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo] participants 16 years of age or older had been followed for a median of 2 months after the second dose.

The safety evaluation in Study 2 is ongoing. The safety population includes participants 16 years of age and older enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Unsolicited Adverse Events

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 (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7,960, placebo = 7,934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. 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 serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

In Study 2 in which 10,841 participants 16 through 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

The higher frequency of reported unsolicited non-serious adverse events among Pfizer-BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by 4 participants in the Pfizer-BioNTech COVID-19 Vaccine 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. No cases of Bell's palsy were reported in the placebo group. 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 Pfizer-BioNTech COVID-19 Vaccine.

Participants 12 Through 15 Years of Age

In an analysis of Study 2, based on data up to the cutoff date of March 13, 2021, 2,260 participants (1,131 Pfizer-BioNTech COVID-19 Vaccine; 1,129 placebo) were 12 through 15 years of age. Of these,

1,308 (660 Pfizer-BioNTech COVID-19 Vaccine and 648 placebo) participants have been followed for at least 2 months after the second dose. The safety evaluation in Study 2 is ongoing.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the participants who received the Pfizer-BioNTech COVID-19 Vaccine, 50.1% were male and 49.9% were female, 85.9% were White, 4.6% were Black or African American, 11.7% were Hispanic/Latino, 6.4% were Asian, and 0.4% were American Indian/Alaska Native.

Unsolicited Adverse Events

In the following analyses of Study 2 in participants 12 through 15 years of age (1,131 of whom received Pfizer-BioNTech COVID-19 Vaccine and 1,129 of whom received placebo), 98.3% of study participants had at least 30 days of follow-up after Dose 2.

Serious Adverse Events

Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients. There were no notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 5.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 5.8% of placebo recipients. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy plausibly related to the study intervention were imbalanced, with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (7) vs. the placebo group (1). There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Participants 5 Through 11 Years of Age

In an analysis of Study 3 Phase 2/3, based on data up to the cutoff date of September 06, 2021, 2,268 participants [1,518 Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA); 750 placebo] were 5 through 11 years of age. Of these, 2,158 (95.1%) [1,444 Pfizer-BioNTech COVID-19 Vaccine and 714 placebo] participants have been followed for at least 2 months after the second dose. An analysis of Study 3 Phase 2/3 adverse event data also included another 2,379 participants [1,591 Pfizer-BioNTech COVID-19 Vaccine and 788 placebo], of whom 71.2% had a follow-up period for at least 2 weeks after Dose 2 up to the cutoff date of October 8, 2021. The safety evaluation in Study 3 is ongoing.

Demographic characteristics in Study 3 were generally similar with regard to age, gender, race, and ethnicity among participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Among the 4,647 participants 5 through 11 years of age who received at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine or placebo, 51.8% were male and 48.2% were female, 77.3% were White, 5.8% were Black or African American, 16.9% were Hispanic/Latino, 8.3% were Asian, and 0.4% were American Indian/Alaska Native.

Unsolicited Adverse Events

In the following analyses of Study 3 in participants 5 through 11 years of age (1,518 of whom received Pfizer-BioNTech COVID-19 Vaccine and 750 of whom received placebo), 99.5% of participants had at least 30 days of follow-up after Dose 2.

Serious Adverse Events

In 1 group of participants (initial enrollment cohort) with a median of 2.3 months follow-up post Dose 2, no serious adverse events were reported that were considered related to vaccination. In a second group of participants (expansion cohort) with a median of 2.4 weeks follow-up post Dose 2, no serious adverse events were reported that were considered related to vaccination.

Non-Serious Adverse Events

In 1 group of participants (initial enrollment cohort), non-serious adverse events from Dose 1 through up to 30 days after Dose 2 up to the cutoff date of September 06, 2021, in ongoing follow-up were reported by 10.9% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 9.1% of placebo recipients. In this group of participants, >99% had follow-up 30 days post Dose 2. In a second group of participants (expansion cohort) for which the median follow-up was 2.4 weeks (range 0 to 3.7 weeks), non-serious adverse events from Dose 1 through the cutoff date of October 8, 2021, were reported by 7.1% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 6.3% of placebo recipients.

In the initial enrollment cohort, from Dose 1 through 30 days after Dose 2, lymphadenopathy was reported in 13 (0.9%) participants in the Pfizer-BioNTech COVID-19 Vaccine group vs. 1 (0.1%) in the placebo group. In the expansion cohort from Dose 1 through the cutoff date, lymphadenopathy was reported in 6 (0.4%) participants in the Pfizer-BioNTech COVID-19 Vaccine group vs. 3 (0.4%) in the placebo group. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Participants 2 Through 4 Years of Age

In an analysis of Study 3 (Phase 2/3), based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 886 participants 2 through 4 years of age who received a 3-dose primary series [606 Pfizer-BioNTech COVID-19 Vaccine (3 mcg modRNA); 280 placebo] were have been followed a median of 1.4 months after the third dose.

Demographic characteristics in Study 3 were generally similar with regard to age, gender, race, and ethnicity among participants 2 through 4 years of age who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Among the 1,835 participants 2 through 4 years of age who received at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine, 49.1% were male and 50.9% were female, 80.1% were White, 14.4% were Hispanic/Latino, 7.1% were multi-racial, 6.9% were Asian, 5.1% were Black or African American, and 0.2% were American Indian/Alaska Native.

Unsolicited Adverse Events

In the following analyses of Study 3 in participants 2 through 4 years of age (606 of whom received Pfizer-BioNTech COVID-19 Vaccine and 280 of whom received placebo), 76.6% of participants had at least 30 days of follow-up after Dose 3.

Serious Adverse Events

Serious adverse events from Dose 1 through 1 month after Dose 3, with an overall median of 1.4 months follow-up after Dose 3 were reported by 0.7% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.9% of placebo recipients. One serious adverse event of fever (maximum temperature 40.3°C) on Day 3 after Dose 2 in a 4-year-old was considered possibly related to vaccination.

Non-Serious Adverse Events

Non-serious adverse events from Dose 1 through up to 30 days after Dose 3, in ongoing follow-up were reported by 18.5% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 18.5% of placebo recipients.

From Dose 1 through 30 days after Dose 3, lymphadenopathy was reported in 1 (0.1%) participant in the Pfizer-BioNTech COVID-19 Vaccine group vs. 0 (0.0%) in the placebo group. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Participants 6 Through 23 Months of Age

In an analysis of Study 3 (Phase 2/3), based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 570 participants 6 through 23 months of age who received a 3-dose primary series [386 Pfizer-BioNTech COVID-19 Vaccine (3 mcg modRNA); 184 placebo] have been followed for a median of 1.3 months after the third dose.

Demographic characteristics in Study 3 were generally similar with regard to age, gender, race, and ethnicity among participants 6 through 23 months of age who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Among the 1,178 participants 6 through 23 months of age who received at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine, 50.0% were male and 50.0% were female, 78.3% were White, 9.9% were multi-racial, 13.7% were Hispanic/Latino, 7.7% were Asian, 3.6% were Black or African American, and 0.3% were American Indian/Alaska Native.

Unsolicited Adverse Events

In the following analyses of Study 3 in participants 6 through 23 months of age (386 of whom received Pfizer-BioNTech COVID-19 Vaccine and 184 of whom received placebo), 83.7% of participants had at least 30 days of follow-up after Dose 3.

Serious Adverse Events

Serious adverse events from Dose 1 through 1 month after Dose 3, with an overall median of 1.3 months follow-up after Dose 3 were reported by 1.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 2.3% of placebo recipients. No serious adverse events were reported that were considered related to vaccination.

Non-Serious Adverse Events

Non-serious adverse events from Dose 1 through up to 1 month after Dose 3, in ongoing follow-up were reported by 29.1% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 26.3% of placebo recipients.

From Dose 1 through 30 days after Dose 3, lymphadenopathy was reported in 2 (0.2%) participants in the Pfizer-BioNTech COVID-19 Vaccine group vs. 0 (0%) in the placebo group. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

First Booster Dose Following a Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 18 through 55 Years of Age

A subset of Study 2 Phase 2/3 participants of 306 participants 18 through 55 years of age received a first booster dose of Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) approximately 6 months (range of 4.8 to 8.0 months) after completing the primary series. Additionally, a total of 23 Study 2 (Phase 1) participants (11 participants 18 through 55 years of age and 12 participants 65 through 85 years of age) received a first booster dose of Pfizer-BioNTech COVID-19 Vaccine approximately 8 months (range 7.9 to 8.8 months) after completing the primary series. Participants 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 through 1 month after vaccination and for serious adverse events for 6 months after the last vaccination.

Among the 306 Phase 2/3 participants, the median age was 42 years (range 19 through 55 years of age), 45.8% were male and 54.2% were female, 81.4% were White, 27.8% were Hispanic/Latino, 9.2% were Black or African American, 5.2% were Asian, and 0.7% were American Indian/Alaska Native. Among the 12 Phase 1 participants 65 through 85 years of age, the median age was 69 years (range 65 through 75 years of age), 6 were male and all were White and Not Hispanic/Latino. Following the booster dose, the median follow-up time was 2.6 months (range 2.1 to 2.9 months) for Phase 1 participants and 2.6 months (range 1.1 to 2.8 months) for Phase 2/3 participants.

Solicited Local and Systemic Adverse Reactions

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of a first booster dose with Pfizer-BioNTech COVID-19 Vaccine for Phase 2/3 participants 18 through 55 years of age.

In participants who received a first booster dose, the mean duration of pain at the injection site was 2.6 days (range 1 to 8 days), for redness 2.2 days (range 1 to 15 days), and for swelling 2.2 days (range 1 to 8 days).

Table 3: Study 2 – Frequency and Percentages of Participants With Solicited Local Adverse Reactions, By Maximum Severity, Within 7 Days After a First Booster Dose of Pfizer-BioNTech COVID-19 Vaccine – Participants 18 through 55 Years of Age*

Solicited Local Adverse Reaction	Pfizer-BioNTech COVID-19 Vaccine[±]
	First Booster Dose N ^a = 289 n ^b (%)
Redness^c	
Any (>2 cm)	17 (5.9)
Mild	10 (3.5)
Moderate	7 (2.4)
Severe	0
Swelling^c	
Any (>2 cm)	23 (8.0)
Mild	13 (4.5)
Moderate	9 (3.1)
Severe	1 (0.3)

Solicited Local Adverse Reaction	Pfizer-BioNTech COVID-19 Vaccine[±]
	First Booster Dose N^a = 289 n^b (%)
Pain at the injection site^d	
Any	240 (83.0)
Mild	174 (60.2)
Moderate	65 (22.5)
Severe	1 (0.3)

Note: Adverse Reactions were collected in the electronic diary (e-diary) from day of vaccination (Day 1) to Day 7 after the booster dose.

Note: No Grade 4 solicited local adverse reactions were reported.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

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.

± Pfizer-BioNTech COVID-19 Vaccine .

Table 4: Study 2 – Frequency and Percentages of Participants With Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days After a First Booster Dose with Pfizer-BioNTech COVID-19 Vaccine – Participants 18 through 55 Years of Age[±]

Solicited Systemic Adverse Reaction	Pfizer-BioNTech COVID-19 Vaccine[±]
	First Booster Dose N^a = 289 n^b (%)
Fever	
≥38.0°C	25 (8.7)
≥38.0°C to 38.4°C	12 (4.2)
>38.4°C to 38.9°C	12 (4.2)
>38.9°C to 40.0°C	1 (0.3)
>40.0°C	0
Fatigue^c	
Any	184 (63.7)
Mild	68 (23.5)
Moderate	103 (35.6)
Severe	13 (4.5)
Headache^c	
Any	140 (48.4)
Mild	83 (28.7)
Moderate	54 (18.7)
Severe	3 (1.0)
Chills^c	
Any	84 (29.1)
Mild	37 (12.8)
Moderate	44 (15.2)
Severe	3 (1.0)

Solicited Systemic Adverse Reaction	Pfizer-BioNTech COVID-19 Vaccine [±]
	First Booster Dose N ^a = 289 n ^b (%)
Vomiting ^d	
Any	5 (1.7)
Mild	5 (1.7)
Moderate	0
Severe	0
Diarrhea ^c	
Any	25 (8.7)
Mild	21 (7.3)
Moderate	4 (1.4)
Severe	0
New or worsened muscle pain ^c	
Any	113 (39.1)
Mild	52 (18.0)
Moderate	57 (19.7)
Severe	4 (1.4)
New or worsened joint pain ^c	
Any	73 (25.3)
Mild	36 (12.5)
Moderate	36 (12.5)
Severe	1 (0.3)
Use of antipyretic or pain medication ^f	135 (46.7)

Note: Adverse reactions and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from day of vaccination (Day 1) to Day 7 after the booster dose.

Note: No Grade 4 solicited systemic adverse reactions were reported.

- a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
 - 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.
- ± Pfizer-BioNTech COVID-19 Vaccine .

In Phase 1 participants ≥ 65 years of age (n = 12), local reaction pain at the injection site (n = 8, 66.7%) and systemic reactions fatigue (n = 5, 41.7%), headache (n = 5, 41.7%), chills (n = 2, 16.7%), muscle pain (n = 4, 33.3%), and joint pain (n = 2, 16.7%) were reported after the booster dose. No participant in this age group reported a severe systemic event or fever after the booster dose.

Unsolicited Adverse Events

Overall, the 306 participants who received a first booster dose, had a median follow-up time of 2.6 months after the booster dose to the cut-off date (June 17, 2021).

In an analysis of all unsolicited adverse events reported following the first booster dose, through 1 month after the booster dose, in participants 18 through 55 years of age (N = 306), those assessed as adverse reactions not

already captured by solicited local and systemic reactions were lymphadenopathy (n = 16, 5.2%), nausea (n = 2, 0.7%), decreased appetite (n = 1, 0.3%), rash (n = 1, 0.3%), and pain in extremity (n = 1, 0.3%).

Serious Adverse Events

Of the 306 participants who received a first booster dose of Pfizer-BioNTech COVID-19 Vaccine, there were no serious adverse events reported from the booster dose through 30 days after the booster dose. One participant reported a serious adverse event 61 days after the booster dose that was assessed as unrelated to vaccination.

First Booster Dose Following a Primary Series of Pfizer-BioNTech COVID-19 in Participants 5 Through 11 Years of Age

A subset of Phase 2/3 participants 5 through 11 years of age received a first booster dose of Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA) at least 5 months after completing the primary series (range 5 to 9 months, 86.8% of participants received a booster dose at least 8 months after Dose 2). Those participants vaccinated prior to February 22, 2022 provided the safety database (n=401), and had a median safety follow-up of 1.3 months from vaccination through the data cut-off date of March 22, 2022.

The median age of these 401 participants was 8.0 years (range 5 through 11 years of age), 52.4% were male and 47.6% were female, 70.1% were White, 7.2% were Black or African American, 22.9% were Hispanic/Latino, 7.7% were Asian, and 2.0% were American Indian/Alaska Native.

Unsolicited Adverse Events

Overall, the 401 participants who received a first booster dose of Pfizer-BioNTech COVID-19 Vaccine had a median follow-up time of 1.3 months after the booster dose through the cutoff date.

In an analysis of all unsolicited adverse events reported in participants 5 through 11 years of age (N = 401) through up to 1 month after a first booster dose, lymphadenopathy (n = 10, 2.5%) was an adverse reaction not already captured by solicited local and systemic reactions.

Serious Adverse Events

No serious adverse events were reported after the first booster dose through the cutoff date.

First Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

The safety of a Pfizer-BioNTech COVID-19 Vaccine booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) booster dose administered following completion of Pfizer-BioNTech COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent National Institutes of Health (NIH) study Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine. In this study, participants who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of 1 of 3 vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported in the study following the Pfizer-BioNTech COVID-19 Vaccine heterologous booster dose

did not identify any new safety concerns, as compared with adverse reactions reported following a Pfizer-BioNTech COVID-19 Vaccine primary series doses or homologous booster dose.

Second Booster Dose Following Primary Series and First Booster Vaccination

Safety surveillance data from the Ministry of Health of Israel on the administration of approximately 700,000 fourth doses of the Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) given at least 4 months after the third dose in participants 18 years of age and older (approximately 600,000 of whom were 60 years of age and older) revealed no new safety concerns.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post authorization use of Pfizer-BioNTech COVID-19 Vaccine. Because these reactions are reported voluntarily, 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)

Nervous System Disorders: syncope, dizziness

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of myocarditis
- Cases of pericarditis
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent 1 of the outcomes listed above

IMPORTANT: When reporting adverse events or vaccine administration errors, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine, Bivalent and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within 1 month prior.
2. In Box 18, description of the event:
 - a. Write “Pfizer-BioNTech COVID-19 Vaccine, Bivalent EUA” as the first line.
 - b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.
3. Contact information:
 - a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
 - b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
 - c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider’s office address).

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below

Website	Email
www.pfizersafetyreporting.com	ARE.AEReporting@pfizer.com

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

No data are available regarding the use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent during pregnancy.

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 Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (modRNA) (30 mcg) and other ingredients included in a single human dose of Pfizer-BioNTech COVID-19 Vaccine 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.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use as a booster dose in individuals 5 through 17 years of age is based on the safety and effectiveness of Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months of age and older and safety and immunogenicity data with the bivalent vaccine (Original and Omicron BA.1) in individuals greater than 55 years of age.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent is not authorized for use in individuals younger than 5 years of age as a booster dose.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older who received the primary series and their data contributes to the overall assessment of safety and effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent [see *Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)*]. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

A clinical study with the bivalent vaccine (Original and Omicron BA.1) included 197 individuals 65 years of age and older and their data contribute to the overall assessment of safety and effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is supplied as a sterile, frozen suspension in single dose and multiple dose vials with gray caps and labels with gray borders.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is formulated to contain 15 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (Original) and 15 mcg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical. Each dose contains 30 mcg modRNA.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent supplied in single dose and multiple dose vials 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 0.19 mg cholesterol), 0.06 mg tromethamine, 0.4 mg tromethamine hydrochloride, and 31 mg sucrose.

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

The effectiveness of a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is based on effectiveness of primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine and immunogenicity of a second booster dose with the bivalent vaccine (Original and Omicron BA.1).

18.1 Efficacy of Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (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 Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) or placebo separated by 21 days. 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 Pfizer-BioNTech COVID-19 Vaccine 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 5 presents the specific demographic characteristics in the studied population.

Table 5: Demographics (population for the primary efficacy endpoint)^a

	Pfizer-BioNTech COVID-19 Vaccine* (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 ^b	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥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 ^c	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^d		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

* Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

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. 100 participants 12 through 15 years of age with limited follow-up in the randomized population received at least 1 dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending

	Pfizer-BioNTech COVID-19 Vaccine* (N=18,242) n (%)	Placebo (N=18,379) n (%)
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on the population analyzed. They contributed to exposure information but with no confirmed COVID-19 cases, and did not affect efficacy conclusions.

c. Includes multiracial and not reported.

d. 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)

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 6.

Table 6: 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	Pfizer-BioNTech COVID-19 Vaccine[±] N^a=18,198 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=18,325 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)
All subjects ^e	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6) ^f
16 through 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
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	Pfizer-BioNTech COVID-19 Vaccine[±] N^a=19,965 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=20,172 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)

All subjects ^c	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3) ^f
16 through 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

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.

± Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

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 through 15 years of age.

f. Credible interval for vaccine efficacy (VE) 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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

18.2 Efficacy of Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 has been performed in approximately 2,200 participants 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cutoff date of March 13, 2021.

The efficacy information in participants 12 through 15 years of age is presented in Table 7.

Table 7: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Participants 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in participants 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	Pfizer-BioNTech COVID-19 Vaccine[±] N^a=1005 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=978 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI)^e
Participants 12 through 15 years of age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in participants 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			

	Pfizer-BioNTech COVID-19 Vaccine[±] N ^a =1119 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Placebo N ^a =1110 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI^e)
Participants 12 through 15 years of age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 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.

± Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

18.3 Immunogenicity of Primary Series of Pfizer-BioNTech COVID-19 Vaccine in Participants 12 Through 15 Years of Age

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing participants 12 through 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 8).

Table 8: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Participants 12 Through 15 Years of Age to Participants 16 Through 25 Years of Age (Immunogenicity Subset) – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID-19 Vaccine*			
		12 Through 15 Years n^a=190	16 Through 25 Years n^a=170	12 Through 15 Years/ 16 Through 25 Years	
Assay	Time Point^b	GMT^c (95% CI^c)	GMT^c (95% CI^c)	GMR^d (95% CI^d)	Met Noninferiority Objective^e (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^f	1 month after Dose 2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic-acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) 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 up to 1 month after Dose 2 were included in the analysis.

* Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

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- a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
 - b. Protocol-specified timing for blood sample collection.
 - c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (12 through 15 years of age minus 16 through 25 years of age) and the corresponding CI (based on the Student t distribution).
 - e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
 - f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

18.4 Immunogenicity of the Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose

In an analysis of a subset from Study 4, a total of 610 participants greater than 55 years of age who had previously received a 2-dose primary series and 1 booster dose with Pfizer-BioNTech COVID-19 Vaccine received 1 of the following as a second booster dose: Pfizer-BioNTech COVID-19 Vaccine or bivalent vaccine (Original and Omicron BA.1). GMRs and seroresponse rates were evaluated at 1 month after vaccination with the bivalent vaccine (Original and Omicron BA.1). The bivalent vaccine (Original and Omicron BA.1) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the first booster dose. The Pfizer-BioNTech COVID-19 Vaccine booster dose was administered 5.3 to 13.1 months (median 6.3 months) after the first booster dose.

The primary objective of the study was to assess superiority with respect to level of 50% neutralizing titer (NT50) and noninferiority with respect to seroresponse rate of the anti-Omicron BA.1 immune response induced by a dose of the bivalent vaccine (Original and Omicron BA.1) relative to the response elicited by a dose of Pfizer-BioNTech COVID-19 Vaccine given as a second booster dose in participants greater than 55 years of age.

A secondary objective of the study was to assess noninferiority with respect to level of NT50 to the Original SARS-COV-2 strain induced by a dose of the bivalent vaccine (Original and Omicron BA.1) relative to the response elicited by a dose of Pfizer-BioNTech COVID-19 Vaccine given as a second booster dose. A comparison of seroresponse rates to the Original strain was descriptive.

Superiority of the anti-Omicron BA.1 NT50 for the bivalent vaccine (Original and Omicron BA.1) relative to Pfizer-BioNTech COVID-19 Vaccine was met, as the lower bound of the 2-sided 95% CI for GMR was >1 . Noninferiority of the anti-Original NT50 for the bivalent vaccine (Original and Omicron BA.1) relative to Pfizer-BioNTech COVID-19 Vaccine was met, as the lower bound of the 2-sided 95% CI for GMR was >0.67 and the point estimate of the GMR was ≥ 0.8 (Table 9).

Non-inferiority of the seroresponse rate to the Omicron BA.1 variant for the bivalent vaccine (Original and Omicron BA.1) relative to Pfizer-BioNTech COVID-19 Vaccine was met as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $>-5\%$ (Table 10). A descriptive summary of seroresponse to the Original strain is also included in Table 10.

Table 9: Study 4 - Geometric Mean Ratios – Participants Without Evidence of Infection Up to 1 Month After the Second Booster Dose – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population

Assay	Vaccine Group (as randomized)	Sampling Time Point ^a	N ^b	GMT (95% CI ^c)	GMR (95% CI ^d)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer) ^e	Pfizer-BioNTech COVID-19 Vaccine	1 month	163	455.8 (365.9, 567.6)	
	Bivalent Vaccine (Original and Omicron BA.1)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)
SARS-CoV-2 neutralization assay - Original strain - NT50 (titer) ^e	Pfizer-BioNTech COVID-19 Vaccine	1 month	182	5998.1 (5223.6, 6887.4)	
	Bivalent Vaccine (Original and Omicron BA.1)	1 month	186	5933.2 (5188.2, 6785.2)	0.99 (0.82, 1.20)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- Protocol-specified timing for blood sample collection.
- n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding row - Pfizer-BioNTech COVID-19 Vaccine) and the corresponding CI (based on the Student t distribution). Superiority for anti-Omicron BA.1 immune response is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1 after satisfying multiplicity adjustment. Noninferiority for anti-Original strain is declared if the lower limit of the 2-sided 95% CI for the GMR is greater than 0.67 (1.5-fold criterion) and the point estimate of the GMR is ≥ 0.8 , after satisfying multiplicity adjustment.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1).

Table 10: Study 4 - Number (%) of Participants Achieving Seroresponse – Participants Without Evidence of Infection Up to 1 Month After the Second Booster Dose – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population

Assay	Vaccine Group (as randomized)	Sampling Time Point ^a	N ^b	n ^c (%) (95% CI ^d)	Difference % ^e (95% CI ^f)
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer) ^g	Pfizer-BioNTech COVID-19 Vaccine	1 month	149	85 (57.0) (48.7, 65.1)	
	Bivalent Vaccine (Original and Omicron BA.1)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)
SARS-CoV-2 neutralization assay - Original strain - NT50 (titer) ^g	Pfizer-BioNTech COVID-19 Vaccine	1 month	179	88 (49.2) (41.6, 56.7)	
	Bivalent Vaccine (Original and Omicron BA.1)	1 month	186	93 (50.0) (42.6, 57.4)	

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group.

Note: Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before the second booster dose). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times \text{LLOQ}$ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

- a. Protocol-specified timing for blood sample collection.
- b. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- c. n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
- d. Exact 2-sided CI based on the Clopper and Pearson method.
- e. Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - Pfizer-BioNTech COVID-19 Vaccine).
- f. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage. Noninferiority for anti-Omicron BA.1 seroresponse is declared if the lower bound of the 2-sided 95% CI for the difference is greater than -5% after satisfying multiplicity adjustment.
- g. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.1).

18.5 Immunogenicity of a First Booster Dose With a Pfizer-BioNTech COVID-19 Vaccine Primary Series in Participants 18 Through 55 Years of Age

Effectiveness of a booster dose of Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 11 and Table 12.

Table 11: Geometric Mean 50% Neutralizing Titer (SARS-CoV-2 USA_WA1/2020) – Comparison of 1 Month After Booster Dose to 1 Month After Primary Series – Participants 18 Through 55 Years of Age Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[±]

Assay	n ^a	1 Month After Booster Dose GMT ^b (95% CI ^b)	1 Month After Primary Series GMT ^b (95% CI ^b)	1 Month After Booster Dose/ 1 Month After Primary Series GMR ^c (97.5% CI ^c)	Met Noninferiority Objective ^d (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^e	212	2466.0 (2202.6, 2760.8)	750.6 (656.2, 858.6)	3.29 (2.77, 3.90)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

Note: Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Pfizer-BioNTech COVID-19 Vaccine) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

± All eligible participants who had received 2 doses of Pfizer-BioNTech COVID-19 Vaccine as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Pfizer-BioNTech COVID-19 Vaccine, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within

an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

- n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥ 0.80 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Table 12: Seroreponse Rate for 50% Neutralizing Titer (SARS-CoV-2 USA_WA1/2020) – Comparison of 1 Month After Booster Dose to 1 Month After Primary Series – Participants 18 Through 55 Years of Age Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population \pm

Assay	N ^a	1 Month After Booster Dose n ^b % (95% CI) ^c	1 Month After Primary Series n ^b % (95% CI) ^c	Difference (1 Month After Booster Dose - 1 Month After Primary Series) % ^d (97.5% CI) ^e	Met Noninferiority Objective ^f (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^g	200	199 99.5 (97.2, 100.0)	196 98.0 (95.0, 99.5)	1.5 (-0.7, 3.7)	Y

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

Note: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times \text{LLOQ}$ is considered a seroreponse.

Note: Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

* Participants who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.

\pm All eligible participants who had received 2 doses of Pfizer-BioNTech COVID-19 Vaccine as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Pfizer-BioNTech COVID-19 Vaccine, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

- N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
- n = Number of participants with seroreponse for the given assay at the given dose/sampling time point.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
- Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
- Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

18.6 Immunogenicity of a First Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

Effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose (30 mcg modRNA) in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose administered following completion of Pfizer-BioNTech COVID-19 Vaccine primary series and from immunogenicity data from an independent NIH study Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine. In this study, participants who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of 1 of 3 vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA). Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer-BioNTech COVID-19 Vaccine was demonstrated regardless of the vaccine used for primary vaccination.

19 HOW SUPPLIED/STORAGE AND HANDLING

Single Dose Vials: Pfizer-BioNTech COVID-19 Vaccine, Bivalent is a suspension for intramuscular injection. Single dose vials with gray caps and labels with gray borders are supplied in a carton containing 10 single dose vials. One vial contains 1 dose of 0.3 mL.

- Carton of 10 single dose vials: NDC 59267-1404-2
- Single dose vial: NDC 59267-1404-1

Multiple Dose Vials: Pfizer-BioNTech COVID-19 Vaccine, Bivalent is a suspension for intramuscular injection. Multiple dose vials with gray caps and labels with gray borders are supplied in a carton containing 10 multiple dose vials. One vial contains 6 doses of 0.3 mL.

- Carton of 10 multiple dose vials: NDC 59267-0304-2
- Multiple dose vial: NDC 59267-0304-1

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

Do not refreeze thawed vials.

Vial Storage Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine, Bivalent may arrive frozen at ultra-cold conditions in thermal containers with dry ice.

Once received, frozen vials may be immediately transferred to the refrigerator [2°C to 8°C (35°F to 46°F)], thawed and stored for up to 10 weeks. The 10-week refrigerated expiry date should be recorded on the carton at the time of transfer. A carton of 10 single dose vials may take up to 2 hours to thaw at this temperature. A carton of 10 multiple dose vials may take up to 6 hours to thaw at this temperature.

Alternatively, frozen vials may be stored in an ultra-low temperature freezer at -90°C to -60°C (-130°F to -76°F) for up to 18 months from the date of manufacture. Do not store vials at -25°C to -15°C (-13°F to 5°F). Once vials are thawed, they should not be refrozen.

If cartons of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are received at 2°C to 8°C (35°F to 46°F), they should be stored at 2°C to 8°C (35°F to 46°F). Check that the carton has been updated to reflect the 10-week refrigerated expiry date.

Regardless of storage condition, the vaccine should not be used after 18 months from the date of manufacture printed on the vial and cartons.

Vial Storage During Use

If not previously thawed at 2°C to 8°C (35°F to 46°F), allow Pfizer-BioNTech COVID-19 Vaccine, Bivalent single dose vials or multiple dose vials to thaw at room temperature [up to 25°C (77°F)] for 30 minutes.

Pfizer-BioNTech COVID-19 Vaccine, Bivalent may be stored at room temperature [8°C to 25°C (46°F to 77°F)] for a total of 12 hours prior to the first puncture. After first puncture, the multiple dose vials should be held between 2°C to 25°C (35°F to 77°F). Multiple dose vials should be discarded 12 hours after first puncture.

Transportation of Vials

If local redistribution is needed, single dose vials and multiple dose vials may be transported at -90°C to -60°C (-130°F to -76°F) or 2°C to 8°C (35°F to 46°F).

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Vaccine Information Fact Sheet for Recipients and Caregivers.

21 CONTACT INFORMATION

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

Website
www.cvdvaccine.com


This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.



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