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2021 Sep-16 AM 11:09
U.S. DISTRICT COURT
N.D. OF ALABAMA

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

AMERICA'S FRONTLINE DOCTORS, *et al.*, Plaintiffs, v. XAVIER BECERRA, *et al.*, Defendants.	CIVIL ACTION NO. 2:21-CV-702-CLM

DECLARATION OF SUZANN BURK

I, Suzann Burk, make the following declaration under oath pursuant to 28 U.S.C. § 1746. I am aware that this declaration will be filed with the United States District Court for the Northern District of Alabama in the case referenced above, and that it is the legal equivalent of a statement under oath, made under penalty of perjury.

1. I am the Director of the Division of Disclosure and Oversight Management ("DDOM"), Office of Communication Outreach and Development, Center for Biologics Evaluation and Research ("CBER"), United States Food and Drug Administration ("FDA"), in Silver Spring, Maryland.

2. As the Director of DDOM, I have overall responsibility for the disclosure of documents officially maintained by CBER, the center in FDA that regulates biologic products such as blood, vaccines, gene therapy, and human cells,

tissues, and cellular and tissue-based products. I have been the Director of DDOM since June 24, 2018. Prior to that date, I was the Team Lead of the Electronic Disclosure Team in DDOM for approximately nine and one-half years. Prior to that, I was a member of the Congressional and Oversight Branch in DDOM for two years and a member of the Access Litigation and Freedom of Information Branch ("ALFOI") in DDOM for four years.

3. In my capacity as Director of DDOM, I have access to official CBER documents. I am responsible for disclosing documents in litigation on behalf of CBER.

4. I submit this declaration in support of Defendants' Motion to Dismiss and Opposition to Plaintiffs' Motion for a Preliminary Injunction in the above-captioned case. The statements made in this declaration are based on my personal knowledge and official records available to me in my official capacity.

5. Attached hereto are copies of the following documents:

Exhibit	**Vaccine Manufacturer**	**Document**	**Date**
1	Pfizer-BioNTech	Fact Sheet for Recipients and Caregivers	May 10, 2021 (revised)
2	Pfizer-BioNTech	Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers)	May 19, 2021 (revised)
3	Pfizer-BioNTech	Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to Pfizer Inc.	May 10, 2021
4	Pfizer-BioNTech	COVID-19 Vaccine Emergency Use Authorization Review Memorandum	Dec. 11, 2020

5	Pfizer-BioNTech	COVID-19 Vaccine EUA Amendment Review Memorandum	May 10, 2021
6	Moderna	Fact Sheet for Recipients and Caregivers	Mar. 26, 2021 (revised)
7	Moderna	Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers)	Mar. 31, 2021 (revised)
8	Moderna	Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to ModernaTX, Inc.	Feb. 25, 2021
9	Moderna	COVID-19 Vaccine Emergency Use Authorization Review Memorandum	Dec. 18, 2020
10	Janssen	Fact Sheet for Recipients and Caregivers	Apr. 23, 2021 (revised)
11	Janssen	Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers)	Apr. 23, 2021 (revised)
12	Janssen	Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to Janssen Biotech, Inc.	June 10, 2021
13	Janssen	COVID-19 Vaccine Emergency Use Authorization Review Memorandum	Feb. 27, 2021

6. I certify that each document listed in Paragraph 5 was the current effective version as of June 10, 2021, and was publicly available on FDA's website, https://www.fda.gov, as of that date.

7. I declare under penalty of perjury that the foregoing Exhibits 1–13 and the facts contained in this declaration are true and correct pursuant to 28 U.S.C. § 1746.

SUZANN BURK
Division Director
Office of Communication
Division of Disclosure and Oversight
Management, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services

Executed on September 16, 2021

CERTIFICATE OF SERVICE

I hereby certify that on September 16, 2021, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF system, which will send notification of such filing to counsel of record.

/s/ James W. Harlow
JAMES W. HARLOW
Senior Trial Attorney

Exhibit 1

Pfizer-BioNTech: Fact Sheet for Recipients and Caregivers (May 10, 2021 (revised))

FACT SHEET FOR RECIPIENTS AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) IN INDIVIDUALS 12 YEARS OF AGE AND OLDER

You are being offered the Pfizer-BioNTech COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, which you may receive because there is currently a pandemic of COVID-19.

The Pfizer-BioNTech COVID-19 Vaccine is a vaccine and may prevent you from getting COVID-19. There is no U.S. Food and Drug Administration (FDA) approved vaccine to prevent COVID-19.

Read this Fact Sheet for information about the Pfizer-BioNTech COVID-19 Vaccine. Talk to the vaccination provider if you have questions. It is your choice to receive the Pfizer-BioNTech COVID-19 Vaccine.

The Pfizer-BioNTech COVID-19 Vaccine is administered as a 2-dose series, 3 weeks apart, into the muscle.

The Pfizer-BioNTech COVID-19 Vaccine may not protect everyone.

This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?

COVID-19 disease is caused by a coronavirus called SARS-CoV-2. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, 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.

WHAT IS THE PFIZER-BIONTECH COVID-19 VACCINE?

The Pfizer-BioNTech COVID-19 Vaccine is an unapproved vaccine that may prevent COVID-19. There is no FDA-approved vaccine to prevent COVID-19.

The FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19 in individuals 12 years of age and older under an Emergency Use Authorization (EUA).

For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE PFIZER-BIONTECH COVID-19 VACCINE?
Tell the vaccination provider about all of your medical conditions, including if you:

- have any allergies
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects your immune system
- are pregnant or plan to become pregnant
- are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

WHO SHOULD GET THE PFIZER-BIONTECH COVID-19 VACCINE?
FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 years of age and older.

WHO SHOULD <u>NOT</u> GET THE PFIZER-BIONTECH COVID-19 VACCINE?
You should not get the Pfizer-BioNTech COVID-19 Vaccine if you:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine.

WHAT ARE THE INGREDIENTS IN THE PFIZER-BIONTECH COVID-19 VACCINE?
The Pfizer-BioNTech COVID-19 Vaccine includes the following ingredients: mRNA, lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

HOW IS THE PFIZER-BIONTECH COVID-19 VACCINE GIVEN?
The Pfizer-BioNTech COVID-19 Vaccine will be given to you as an injection into the muscle.

The Pfizer-BioNTech COVID-19 Vaccine vaccination series is 2 doses given 3 weeks apart.

If you receive one dose of the Pfizer-BioNTech COVID-19 Vaccine, you should receive a second dose of this same vaccine 3 weeks later to complete the vaccination series.

HAS THE PFIZER-BIONTECH COVID-19 VACCINE BEEN USED BEFORE?
The Pfizer-BioNTech COVID-19 Vaccine is an unapproved vaccine. In clinical trials, approximately 23,000 individuals 12 years of age and older have received at least 1 dose of the Pfizer-BioNTech COVID-19 Vaccine.

WHAT ARE THE BENEFITS OF THE PFIZER-BIONTECH COVID-19 VACCINE?
In an ongoing clinical trial, the Pfizer-BioNTech COVID-19 Vaccine has been shown to prevent COVID-19 following 2 doses given 3 weeks apart. The duration of protection against COVID-19 is currently unknown.

WHAT ARE THE RISKS OF THE PFIZER-BIONTECH COVID-19 VACCINE?
There is a remote chance that the Pfizer-BioNTech COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Pfizer-BioNTech COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Dizziness and weakness

Side effects that have been reported with the Pfizer-BioNTech COVID-19 Vaccine include:

- severe allergic reactions
- non-severe allergic reactions such as rash, itching, hives, or swelling of the face
- injection site pain
- tiredness
- headache
- muscle pain
- chills
- joint pain
- fever
- injection site swelling
- injection site redness
- nausea
- feeling unwell
- swollen lymph nodes (lymphadenopathy)
- diarrhea
- vomiting
- arm pain

These may not be all the possible side effects of the Pfizer-BioNTech COVID-19 Vaccine. Serious and unexpected side effects may occur. Pfizer-BioNTech COVID-19 Vaccine is still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?
If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Call the vaccination provider or your healthcare provider if you have any side effects that bother you or do not go away.

Report vaccine side effects to FDA/CDC Vaccine Adverse Event Reporting System (VAERS). The VAERS toll-free number is 1-800-822-7967 or report online to https://vaers.hhs.gov/reportevent.html. Please include "Pfizer-BioNTech COVID-19 Vaccine EUA" in the first line of box #18 of the report form.

In addition, you can report side effects to Pfizer Inc. at the contact information provided below.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

You may also be given an option to enroll in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information on how to sign up, visit: www.cdc.gov/vsafe.

WHAT IF I DECIDE NOT TO GET THE PFIZER-BIONTECH COVID-19 VACCINE?
It is your choice to receive or not receive the Pfizer-BioNTech COVID-19 Vaccine. Should you decide not to receive it, it will not change your standard medical care.

ARE OTHER CHOICES AVAILABLE FOR PREVENTING COVID-19 BESIDES PFIZER-BIONTECH COVID-19 VACCINE?
Currently, there is no approved alternative vaccine available for prevention of COVID-19. Other vaccines to prevent COVID-19 may be available under Emergency Use Authorization.

CAN I RECEIVE THE PFIZER-BIONTECH COVID-19 VACCINE WITH OTHER VACCINES?
There is no information on the use of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?
If you are pregnant or breastfeeding, discuss your options with your healthcare provider.

WILL THE PFIZER-BIONTECH COVID-19 VACCINE GIVE ME COVID-19?
No. The Pfizer-BioNTech COVID-19 Vaccine does not contain SARS-CoV-2 and cannot give you COVID-19.

KEEP YOUR VACCINATION CARD
When you get your first dose, you will get a vaccination card to show you when to return for your second dose of Pfizer-BioNTech COVID-19 Vaccine. Remember to bring your card when you return.

ADDITIONAL INFORMATION
If you have questions, visit the website or call the telephone number provided below.

To access the most recent Fact Sheets, please scan the QR code provided below.

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

HOW CAN I LEARN MORE?
- Ask the vaccination provider.
- Visit CDC at https://www.cdc.gov/coronavirus/2019-ncov/index.html.
- Visit FDA at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.
- Contact your local or state public health department.

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?
The vaccination provider may include your vaccination information in your state/local jurisdiction's Immunization Information System (IIS) or other designated system. This will ensure that you receive the same vaccine when you return for the second dose. For more information about IISs visit: https://www.cdc.gov/vaccines/programs/iis/about.html.

CAN I BE CHARGED AN ADMINISTRATION FEE FOR RECEIPT OF THE COVID-19 VACCINE?
No. At this time, the provider cannot charge you for a vaccine dose and you cannot be charged an out-of-pocket vaccine administration fee or any other fee if only receiving a COVID-19 vaccination. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients).

WHERE CAN I REPORT CASES OF SUSPECTED FRAUD?
Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or https://TIPS.HHS.GOV.

WHAT IS THE COUNTERMEASURES INJURY COMPENSATION PROGRAM?
The Countermeasures Injury Compensation Program (CICP) is a federal program that may help pay for costs of medical care and other specific expenses of certain people who have been seriously injured by certain medicines or vaccines, including this vaccine. Generally, a claim must be submitted to the CICP within one (1) year from the date of receiving the vaccine. To learn more about this program, visit www.hrsa.gov/cicp/ or call 1-855-266-2427.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?
The United States FDA has made the Pfizer-BioNTech COVID-19 Vaccine available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

The Pfizer-BioNTech COVID-19 Vaccine has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that the product may be effective to prevent COVID-19 during the COVID-19 pandemic and that the known and potential benefits of the product outweigh the known and potential risks of the product. All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for the Pfizer-BioNTech COVID-19 Vaccine is in effect for the duration of the COVID-19 EUA declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

Manufactured by
Pfizer Inc., New York, NY 10017

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

LAB-1451-4.2a
Revised: 10 May 2021

Scan to capture that this Fact Sheet was provided to vaccine recipient for the electronic medical records/immunization information systems.

Barcode Date: 05/2021

Exhibit 2

Pfizer-BioNTech: Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) (May 19, 2021 (revised))

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

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**, for active immunization to prevent COVID-19 in individuals 12 years of age and older.

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 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. See “MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION” for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

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 for active immunization against 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

Storage and Handling

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF) until the expiry date printed on the label. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned one time to the recommended storage condition of -80ºC to -60ºC (-112ºF to -76ºF). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

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

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

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

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

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

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

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

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

Dose Preparation

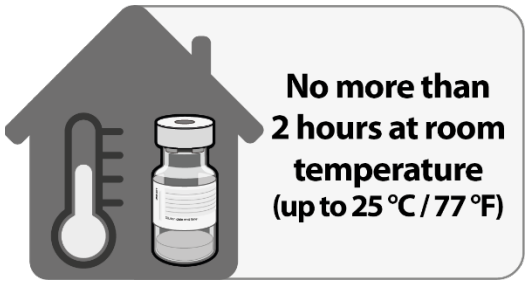
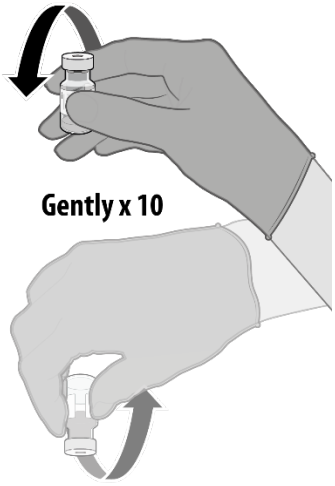
Prior to Dilution
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *(see Storage and Handling)*.
- Refer to thawing instructions in the panels below.

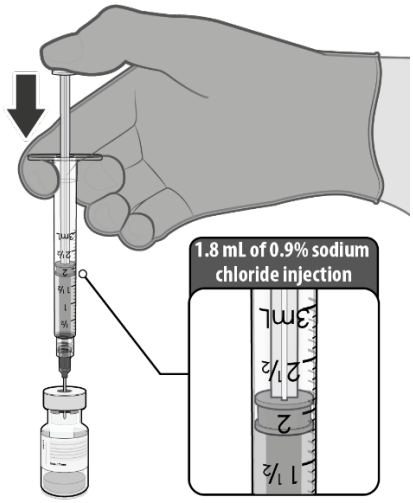
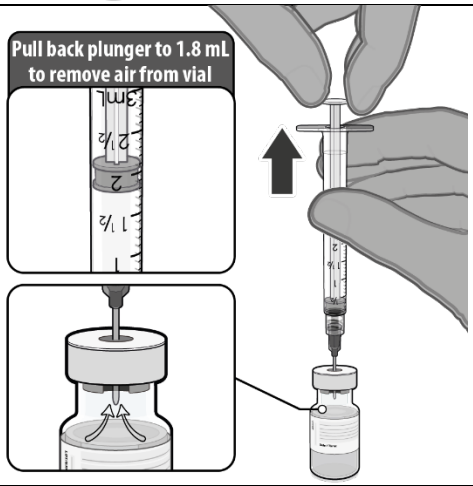
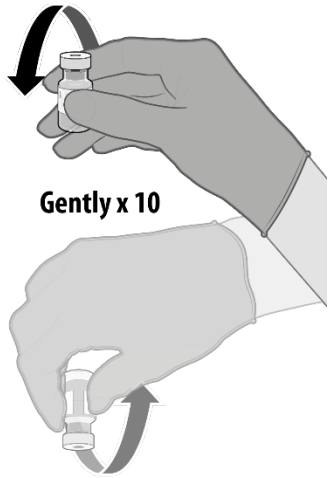
Dilution
Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine

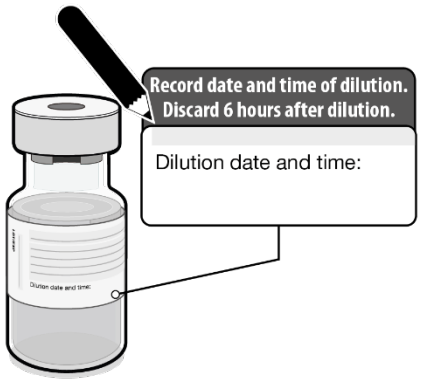
and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not add more than 1.8 mL of diluent.

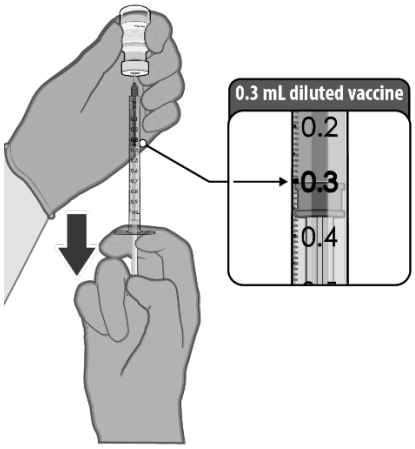
After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: ○ Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month. ○ Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.

DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.
	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.

	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or needle. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Administer immediately.

Administration

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

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

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

Contraindications

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

Warnings

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.

Monitor Pfizer-BioNTech COVID-19 Vaccine 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).

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.

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

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

Adverse Reactions

Adverse Reactions in Clinical Trials
Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy *(see Full EUA Prescribing Information)*.

Adverse Reactions in Post Authorization Experience
Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), diarrhea, vomiting, and pain in extremity (arm) have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.

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

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine 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 "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving each dose of Pfizer-BioNTech COVID-19 Vaccine, including:

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

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

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

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, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine 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 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 or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
    - vaccine administration errors whether or not associated with an adverse event,
    - serious adverse events* (irrespective of attribution to vaccination),
    - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
    - cases of COVID-19 that result in hospitalization or death.

    Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, 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 to recipients.

* 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 one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

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 Fact Sheets, please scan the QR code provided below.

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

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM

This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or https://TIPS.HHS.GOV.

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, for active immunization against COVID-19 in individuals 12 years of age and older.

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

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 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 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.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Pfizer

Manufactured by
Pfizer Inc., New York, NY 10017

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

LAB-1450-8.2b

Revised: 19 May 2021

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

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

* 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 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.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

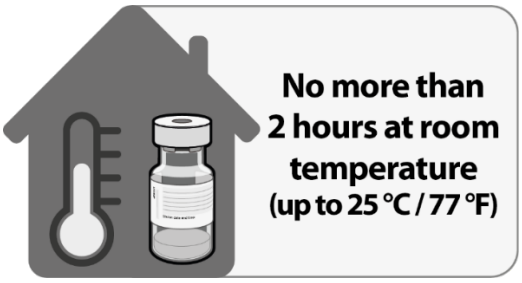
Prior to Dilution

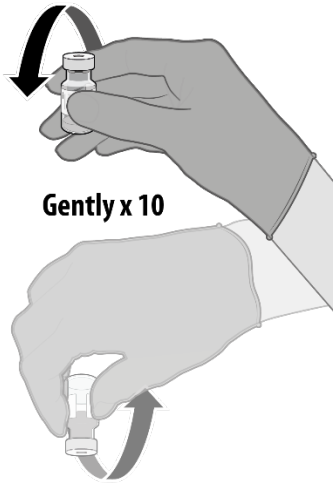
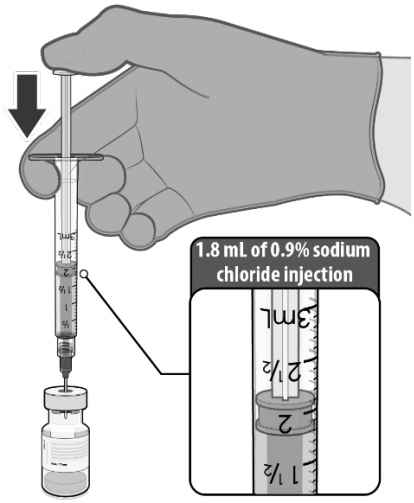
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *[see How Supplied/Storage and Handling (19)]*.
- Refer to thawing instructions in the panels below.

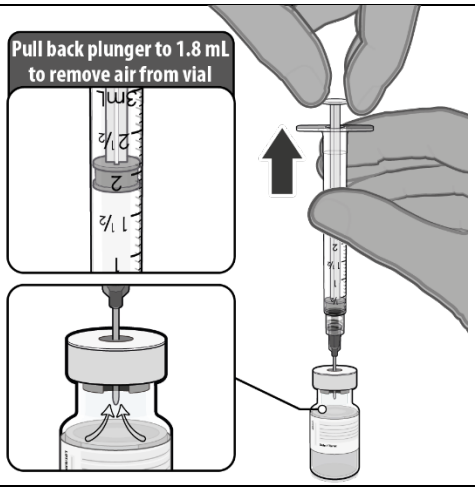
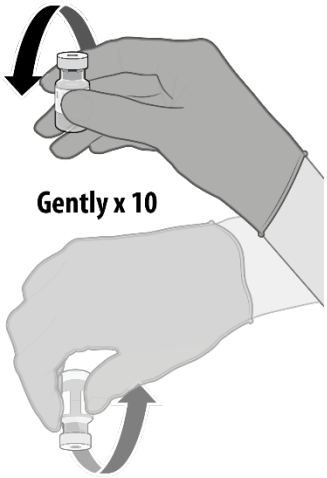
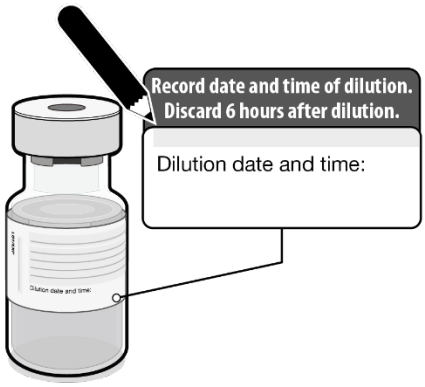
Dilution

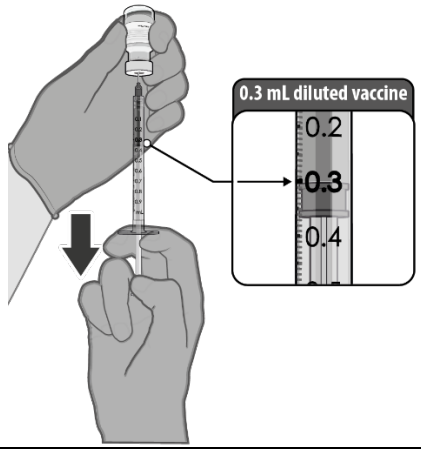
- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not add more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	

	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by:
	  ○ Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month.
	  ○ Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes.
	• Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

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

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using low dead-volume syringes and/or needles. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Administer immediately.

2.2 Administration Information

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

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

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

2.3 Vaccination Schedule for Individuals 12 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

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

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

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

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

5.2 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.

5.3 Altered Immunocompetence

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

5.4 Limitation of Effectiveness

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

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, 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. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

In a clinical study, adverse reactions in adolescents 12 through 15 years of age included pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%).

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials.

6.1 Clinical Trials Experience

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

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 12 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-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 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively) and 2,260 adolescents are 12 through 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively).

In Study 2, all participants 12 to <16 years of age, and participants 16 years of age and older in the reactogenicity subset, were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination]. Tables 1 through 6 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID 19 Vaccine and placebo.

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 of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants 16 years 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.

Solicited Local and Systemic Adverse Reactions

Across both age groups, 18 through 55 years of age and 56 years and older, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Redness[c]				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[c]				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site[d]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue[c]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Headache[c]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[c]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[d]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[e]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[c]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication[f]	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

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

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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

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

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Redness[c]				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[c]				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

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

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Headache[c]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[c]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[d]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[e]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[c]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

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

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

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 and presented in Tables 3 and 4. 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 four 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.

Adolescents 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 adolescents (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) adolescents have been followed for at least

2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine. 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 adolescents who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the adolescents 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.

Solicited Local and Systemic Adverse Reactions

The mean duration of pain at the injection site after Dose 1 was 2.4 days (range 1 to 10 days), for redness 2.4 days (range 1 to 16 days), and for swelling 1.9 days (range 1 to 5 days) for adolescents in the Pfizer-BioNTech COVID-19 Vaccine group.

Table 5: Study 2 – Frequency and Percentages of Adolescents With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1127 n[b] (%)	**Placebo Dose 1 N[a]=1127 n[b] (%)**	**Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1097 n[b] (%)**	**Placebo Dose 2 N[a]=1078 n[b] (%)**
Redness[c]				
Any (>2 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling[c]				
Any (>2 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain at the injection site[d]				
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 6: Study 2 – Frequency and Percentages of Adolescents with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1127 n[b] (%)	Placebo Dose 1 N[a]=1127 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1097 n[b] (%)	Placebo Dose 2 N[a]=1078 n[b] (%)
Fever				
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache[c]				
Any	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills[c]				
Any	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting[d]				
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0 (0.0)	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea[e]				
Any	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain[c]				
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1127 n[b] (%)	Placebo Dose 1 N[a]=1127 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1097 n[b] (%)	Placebo Dose 2 N[a]=1078 n[b] (%)
New or worsened joint pain[c]				
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Use of antipyretic or pain medication[f]	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

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

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

Unsolicited Adverse Events

In the following analyses of Study 2 in adolescents 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.

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.

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

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 Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- 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 one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, 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
- 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 and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Pfizer-BioNTech COVID-19 Vaccine 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).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

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

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on 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 (mRNA) (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 four 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 on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 12 through 18 years of age is based on safety and effectiveness data in this age group and in adults.

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine does not include use in individuals younger than 12 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[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.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine 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 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

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with 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 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 7 presents the specific demographic characteristics in the studied population.

Table 7: 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)

	Pfizer-BioNTech COVID-19 Vaccine (N=18,242) n (%)	Placebo (N=18,379) n (%)
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)

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 one dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending 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/m^2)
- 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 8.

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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine N[a]=18,198 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All 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 n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All subjects[e]	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.

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 adolescents 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 in Adolescents 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 has been performed in approximately 2,200 adolescents 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 adolescents 12 through 15 years of age is presented in Table 9.

Table 9: 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, Adolescents 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 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])**
Adolescents 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 adolescents 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])**
Adolescents 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.

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 in Adolescents 12 Through 15 Years of Age

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing adolescents 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 10).

Table 10: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Adolescents 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.

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 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12 through 15 years of age] – Group 2 [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 50% neutralization titers (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.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF) until the expiry date printed on the label. Alternatively, vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept

frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned one time to the recommended storage condition of -80ºC to -60ºC (-112ºF to -76ºF). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

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

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

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

Vials must reach room temperature before dilution.

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

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

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

20 PATIENT COUNSELING INFORMATION

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

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

21 CONTACT INFORMATION

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

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

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

Manufactured by
Pfizer Inc., New York, NY 10017

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

LAB-1457-8.2b

Revised: 19 May 2021

Exhibit 3

Pfizer-BioNTech: Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to Pfizer Inc. (May 10, 2021)

May 10, 2021

Pfizer Inc.
Attention: Ms. Elisa Harkins
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Harkins:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 for individuals 16 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization twice: December 23, 2020[3] and February 25, 2021.[4]

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] In the December 23, 2020 revision, FDA removed reference to the number of doses per vial after dilution from the letter of authorization, clarified the instructions for vaccination providers reporting to VAERS, and made other technical corrections. FDA also revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to clarify the number of doses of vaccine per vial after dilution and the instructions for reporting to VAERS. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers were revised to include additional information on safety monitoring and to clarify information about the availability of other COVID-19 vaccines.

[4] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by Pfizer Inc. The Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers) was revised to provide an update to the storage and transportation temperature for frozen vials, direct the provider to the correct CDC website for information on monitoring vaccine recipients for the occurrence of immediate adverse reactions, to include data from a developmental toxicity study, and add adverse reactions that have been identified during post authorization use. The Fact Sheet for Recipients and Caregivers was revised to add adverse reactions that have been identified during post authorization use.

On May 10, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA again is reissuing the letter in its entirety to authorize emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 for individuals 12 through 15 years of age, as well as for individuals 16 years of age and older. With authorization of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) is being revised to include the following Warning: "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." The Fact Sheet for Recipients and Caregivers is being revised to instruct vaccine recipients or their caregivers to tell the vaccination provider about fainting in association with a previous injection.

Pfizer-BioNTech COVID-19 Vaccine is for use for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid particles. It is an investigational vaccine not licensed for any indication.

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and efficacy data from an ongoing phase 1/2/3 trial in approximately 44,000 participants randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. The trial has enrolled participants 12 years of age and older. FDA's review at that time considered the safety and effectiveness data as they relate to the request for emergency use authorization in individuals 16 years of age and older. FDA's review of the available safety data from 37,586 of the participants 16 years of age and older, who were followed for a median of two months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the available efficacy data from 36,523 participants 12 years of age and older without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirmed the vaccine was 95% effective (95% credible interval 90.3, 97.6) in preventing COVID-19 occurring at least 7 days after the second dose (with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group). Based on these data, and review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 16 years of age and older. Finally, on December 10, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the May 10, 2021 authorization for individuals 12 through 15 years of age, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial that has enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 years of age. Trial participants were randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or

saline control. FDA's review of the available safety data from 2,260 participants 12 through 15 years of age, who were followed for a median of 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose of Pfizer-BioNTech COVID-19 Vaccine in a subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection confirm the geometric mean antibody titer in participants 12 through 15 years of age was non-inferior to the geometric mean antibody titer in participants 16 through 25 years of age. FDA's analysis of available descriptive efficacy data from 1,983 participants 12 through 15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 100% effective (95% confidence interval 75.3, 100.0) in preventing COVID-19 occurring at least 7 days after the second dose (with no COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 12 through 15 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 12 through 15 years of age.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

3. There is no adequate, approved, and available alternative to the emergency use of Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[5]

II. Scope of Authorization

[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Pfizer Inc. will supply Pfizer-BioNTech COVID-19 Vaccine either directly or through authorized distributor(s)[6], to emergency response stakeholders[7] as directed by the U.S. government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA;
- The Pfizer-BioNTech COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[8] and used only to prevent COVID-19 in individuals ages 12 and older; and
- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

Product Description

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

[6] "Authorized Distributor(s)" are identified by Pfizer Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Pfizer-BioNTech COVID-19 Vaccine.

[7] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

[8] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection) contributes an additional 2.16 mg sodium chloride per dose.

The dosing regimen is two doses of 0.3 mL each, 3 weeks apart.

The manufacture of the authorized Pfizer-BioNTech COVID-19 Vaccine is limited to those facilities identified and agreed upon in Pfizer's request for authorization.

The Pfizer-BioNTech COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Pfizer-BioNTech COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19)

- Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 12 Years of Age and Older

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine, when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Pfizer-BioNTech COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Pfizer-BioNTech COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19 in individuals 12 years of age and older as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer Inc. and Authorized Distributor(s)

A. Pfizer Inc. and authorized distributor(s) will ensure that the authorized Pfizer-BioNTech COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Pfizer Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Pfizer Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving authorized Pfizer-BioNTech COVID-19 Vaccine. Pfizer Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets for the Pfizer COVID-19 Vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for

Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[9]

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in children and adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
- Newly identified safety concerns in the interval; and
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by the Agency.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

[9] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report. The first report is due July 2021.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (12 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Pfizer-BioNTech COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Pfizer-BioNTech COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose.

T. Vaccination providers administering Pfizer-BioNTech COVID-19 Vaccine must report the following information associated with the administration of Pfizer-BioNTech COVID-19 Vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):

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

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

U. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine clearly and conspicuously shall state that:
- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 12 years of age and older; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

_____

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Exhibit 4

Pfizer-BioNTech: COVID-19 Vaccine Emergency Use Authorization Review Memorandum (Dec. 11, 2020)

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	27034
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	November 20, 2020
Receipt Date	November 20, 2020
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Nabil Al-Humadi, Ph.D., Toxicology reviewer, OVRR/DVRPA; Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Laura Fontan, Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	December 11, 2020
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.3 mL Suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 16 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	chemistry, manufacturing, and controls
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA for a COVID-19 vaccine after determining that certain statutory requirements are met.

On November 20, 2020, the Sponsor (Pfizer, on behalf of Pfizer and BioNTech) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 and in preventing COVID-19 following the first dose, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020, data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ⩾55 years of age (⩽ 2.8%) as compared to younger participants (⩽4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the

vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis will be further evaluated as part of the pharmacovigilance plan for the vaccine.

Non-clinical toxicology studies with BNT162b did not raise specific safety concerns, and other non-clinical studies support the vaccine's immunogenicity, reduction of SARS-CoV-2 pulmonary viral load in animal challenge models, and absence of findings suggesting risk of vaccine-enhanced disease.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on December 10, 2020. Following a discussion of the data presented, the VRBPAC voted 17-4 (with one abstention) in favor of the determination that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 10, 2020, meeting, the review team concludes that:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine (BNT162b) may be effective to prevent such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

- The known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.
- There is no adequate, approved, and available alternative to the product for preventing COVID-19 caused by SARS-CoV-2.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of HHS declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. Available Therapies for COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use

authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.3. EUA Request for the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 μg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A Phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 μg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.4. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least

one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

2.5. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6] These considerations are summarized below.

Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse

events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk review and assessment to support continuation of the EUA.

Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

3. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

3.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

3.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older."

4. FDA Review of Clinical Safety and Effectiveness Data

4.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 µg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

4.2. Study C4591001

4.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a Phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In Phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels

in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from Phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into Phase 2/3.

In Phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion. The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary efficacy endpoints

Study C4591001 has two primary endpoints:

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- 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.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

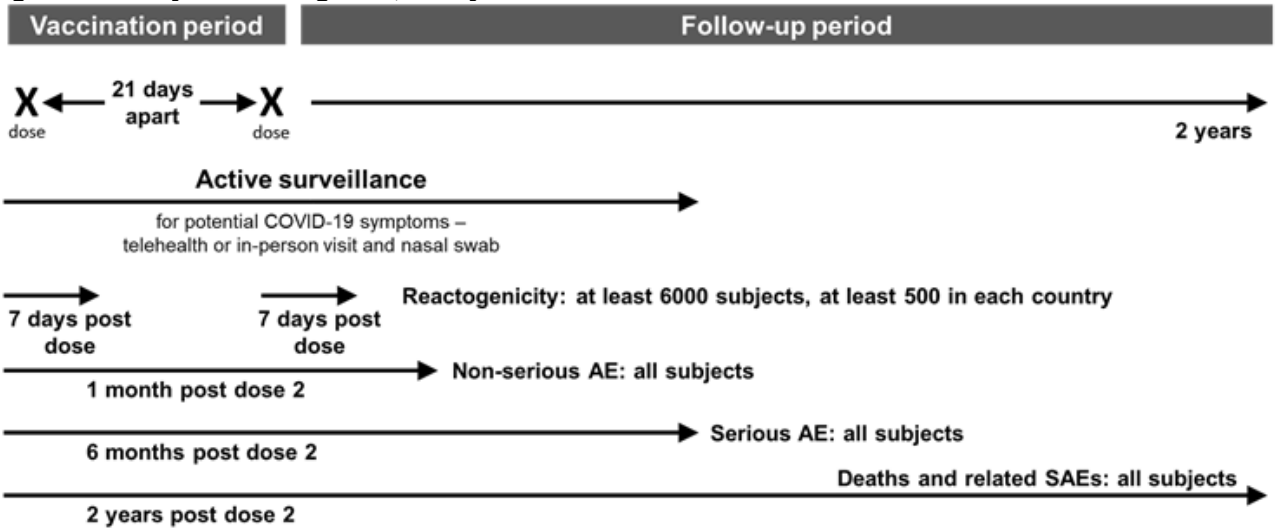
- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)

- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All Phase 1 participants (n=30), and then 6653 U.S. participants (360 Phase 2, 6293 Phase 3) and the first ~500 Phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. For all participants, unsolicited adverse events (AEs) were collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. As of the data cutoff date, reactogenicity assessed as solicited reactions and events are available from a limited number of adolescents 16 and 17 years of age, since enrollment for this age group began with implementation of Protocol Amendment 6 (finalized September 8, 2020) and the Phase 2/3 safety population only participants 16 and 17 years of age enrolled by October 9, 2020. Adolescents enrolled after implementation of Protocol Amendment 9 (finalized 29 October 2020) were included in the reactogenicity subset. For any Phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 Phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were

insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in Phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In Phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The

percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the Phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

4.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the Phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the Phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller Phase 2/3 safety population.

4.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (Phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment

groups. Of 43,448 participants in the Phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

Table 2. Efficacy Populations, Treatment Groups as Randomized

Population	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a] n = Number of participants with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
[c] Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Population	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the Phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020, data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the Phase 2/3 safety population analyses.

4.2.4. Demographics and Other Baseline Characteristics

Overall, the Phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The population for the analysis of the primary efficacy endpoint (evaluable efficacy population) 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. The demographic characteristics among vaccine and placebo participants in the each of the efficacy populations were similar. The demographics of the evaluable efficacy population used for the second primary endpoint is displayed in Table 4.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 N[a]=20033 n[b] (%)	Placebo N[a]=20244 n[b] (%)	Total N[a]=40277 n[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity only (BMI ≥30 kg/m^2).

Overall, the Phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and Phase 2/3 safety population with median 2-month follow-up.

Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or Other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

4.2.5. Vaccine Efficacy

Primary efficacy analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

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 to 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
>55 years	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

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

[d] n2 = Number of participants at risk for the endpoint.

[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.

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

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7).

The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With and Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

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

[d] n2 = Number of participants at risk for the endpoint.

[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.

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

Subgroup analyses of vaccine efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or Other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[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 VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f] At risk is defined as having at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity (BMI ≥30 kg/m^2).
[g] Obese is defined as BMI ≥30 kg/m^2.
[h] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 N[a]=8 n[b] (%)	Placebo N[a]=162 n[b] (%)	Total N[a]=170 n[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or obesity only (BMI ≥30 kg/m^2).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection). However, available data are insufficient to determine whether such individuals could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

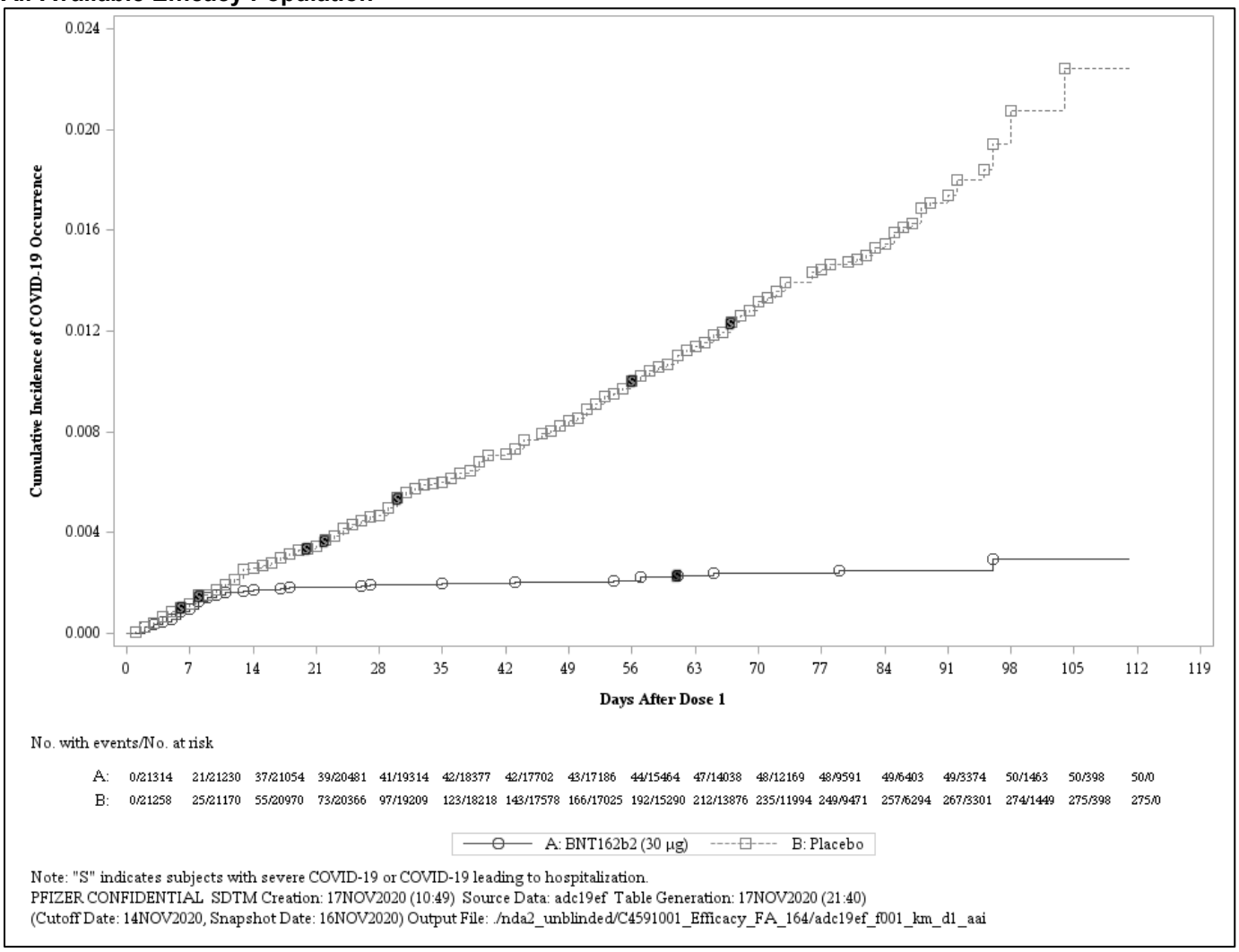
Efficacy Endpoint Subgroup	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days 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 prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix A, page 57) category or BMI ≥30 kg/m2.

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Secondary efficacy analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2, Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 6 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[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 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional efficacy analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint, All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after	50	275	82.0
Dose 1 – Dose 1	4.015 (21314)	3.982 (21258)	(75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 6 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[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 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned final primary efficacy analysis, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (⩾93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

4.2.6. Safety

Overview of adverse events

Table 14 below presents an overview of all adverse events in the Phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview, Ages 16 Years and Older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the Phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the Phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited local reactions and systemic adverse events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population, 18 to 55 Years of Age*

Local Reaction	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
*Includes <10 participants 16 and 17 years of age.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population, 18 to 55 Years of Age*

Adverse Event	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0°C to ≤38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to ≤38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to ≤40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

Adverse Event	BNT162b2 Dose 1 N=2291 n (%)	Placebo Dose 1 N=2298 n (%)	BNT162b2 Dose 2 N=2098 n (%)	Placebo Dose 2 N=2103 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] 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.
*Includes <10 participants 16 and 17 years of age.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to ≤38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to ≤38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to ≤40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] 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.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the Phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020, data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited Local Reactions and Systemic Adverse Events Reported Within 7 Days After Each Dose, Phase 2/3 Safety Population, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 Dose 1 N=53 n (%)	Placebo Dose 1 N=50 n (%)	BNT162b2 Dose 2 N=53 n (%)	Placebo Dose 2 N=50 n (%)
General disorders and administration site conditions	4 (7.5%)	4 (8.0%)	5 (9.4%)	2 (4.0%)
Injection site pain	3 (5.7)	2 (4.0)	3 (5.7)	0 (0.0)
Fatigue	1 (1.9)	1 (2.0)	1 (1.9)	1 (2.0)
Pyrexia	1 (1.9)	0 (0.0)	4 (7.5)	0 (0.0)
Chills	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)
Headache	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 N=4058 n (%)	Placebo N=4043 n (%)	Total N=8101 n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)

System Organ Class Preferred Term	BNT162b2 N=4058 n (%)	Placebo N=4043 n (%)	Total N=8101 n (%)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the Phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

During review of the EUA request, FDA became aware of two cases of anaphylactic reactions in vaccine recipients during the start of the vaccination campaign in the United Kingdom following authorization of the vaccine in that country (approximately 15,000 individuals vaccinated). These reactions were reported to have occurred in the immediate post-vaccination period in individuals with medical history of anaphylactic reactions and required treatment with epinephrine. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. On further review of hypersensitivity-related adverse events in the BNT162b development program, none occurred during the immediate post-vaccination period, none required epinephrine treatment, and none were otherwise classified as serious (i.e., no reported events of anaphylactoid reactions in the clinical trials). Participants in clinical trials were excluded if they had a history of significant allergic reaction to any vaccine or component of BNT162b but were not excluded for history of other significant allergic reactions.

Immediate AEs (Phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%). For both study groups, no participant reported an immediate allergic reaction related to vaccination or to the saline placebo.

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs

in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious adverse events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other participant had pre-existing atherosclerotic disease and baseline obesity and died 3 days after vaccination #1 The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study

intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3,410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1,594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020, (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 6 participants (4 vaccine, 2 placebo), within 30 days after LMP in 10 participants (4 vaccine, 6 placebo), >30 days after LMP in 2 participants (0 vaccine, 2 placebo), and date of LMP not known in 5

participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise unknown at this time.

Clinical laboratory evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 Phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 Phase 1 participants who received the 30-µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 2/3 safety population (N=37,586; 18,801 vaccine,18,785 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations described in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43,448; 21,720 vaccine, 21,728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest 60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine.

4.3. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, Phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was September 17, 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was September 18, 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

5. FDA Review of Other Information Submitted in Support of the EUA

5.1. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

5.2. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include anaphylaxis (including anaphylactic reactions) as an important potential risk and missing information in pediatric

participants less than 16 years of age. Division of Epidemiology recommendations are as follows:

- Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
  - Vaccine administration errors whether or not associated with an adverse event
  - Serious adverse events (irrespective of attribution to vaccination)
  - Cases of Multisystem Inflammatory Syndrome in children and adults
  - Cases of COVID-19 that result in hospitalization or death
- The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
  - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest (AESIs)
  - Newly identified safety concerns in the interval
  - Actions taken since the last report because of adverse experiences (for example, changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)
- Pfizer, Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of AESIs, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general US population (16 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, and subpopulations with specific comorbidities. The study should be conducted in large scale databases with an active comparator. Pfizer, Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates. The Sponsor has proposed the following three planned active surveillance studies:
  - Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry about AESI, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents will receive follow-up surveys for a 30-month period.
  - Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated subjects will be compared to unvaccinated comparators. The study will be conducted for 30 months.
  - Study Protocol Number C4591012. This study is an active surveillance study for AESIs and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated subjects will be compared to unvaccinated subjects or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Mandatory reporting by vaccination providers to VAERS for the following events:
  - Vaccine administration errors whether or not associated with an adverse event
  - Serious adverse events (irrespective of attribution to vaccination)
  - Cases of Multisystem Inflammatory Syndrome in children and adults
  - Cases of COVID-19 that result in hospitalization or death

- Active surveillance of vaccine recipients via the v-safe program. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

5.3. Non-Clinical Studies

Toxicology studies

To support their EUA request, Pfizer submitted the following general toxicology studies:

- Repeat-dose toxicity study of three LNP-formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Wistar Han rats. Study number: 38166. Reviewed under IND 19736 amendments 0 and 32.

- 17-day intramuscular toxicity study of BNT162B2 (V9) and BNT162B3C In Wistar Han rats with a 3-week recovery. Study number: 20GR142. Reviewed under IND 19736 amendment 141.

Based on nonclinical toxicity assessments, there are no significant safety issues to report. The following DART study is still in progress and will be reviewed when submitted: Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat.

Other non-clinical studies

Several nonclinical studies in mice and rhesus macaques were conducted to support the safety and efficacy of BNT162b2. BNT162b2 was highly immunogenic in mice with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4+ response, as well as an IFNγ+, IL-2+, CD8+ T-cell response, after a single immunization. BNT162b2 was also assessed for immunogenicity and for protection against an infectious SARS-CoV-2 challenge in rhesus macaques. Rhesus macaques immunized intramuscularly had readily detectable S1-binding IgG and SARS-CoV-2 neutralizing titers (NT_{50}) as early as 14 days after a single immunization, with substantial increases following the second immunization. Animals were challenged with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-

WA1/2020) and there was a significant decrease in viral RNA detection in bronchoalveolar lavage fluid in the BNT162b2-immunized macaques as compared with the control-immunized rhesus macaques. Further, there was no radiographic evidence of vaccine-elicited enhanced disease in immunized animals. Based on current hypotheses regarding the etiology of vaccine-associated enhanced disease, the provided data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice and rhesus macaques; (2) the Th1 bias in T cell responses; and (3) the lack of disease in vaccinated rhesus macaques challenged with SARS-CoV-2.

5.4. Chemistry, Manufacturing, and Control (CMC) Information

The manufacturing process for the BNT162b2 drug substance (DS) consists of two major steps: (b) (4) . The BNT162b2 drug product (DP) is manufactured by mixing the modRNA DS with lipids during lipid particle (LNP) formulation followed by fill/finish. To support the EUA request, in-process, release, and characterization data for a minimum of three process performance qualification (PPQ) DS batches for each DS manufacturing facility were provided. Certificates of Analysis (CoAs) for a minimum of three GMP commercial-scale DP lots from each DP manufacturing node were requested from the Sponsor to demonstrate DP process performance and consistency. DP data from four manufacturing nodes were available during the EUA review. In addition, to support vaccine supply and availability, data from two additional nodes will be submitted to the EUA between December 17 and December 23, 2020. Once authorized, the Sponsor will submit the CoAs of DP lots to be distributed under EUA for review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent changes during vaccine development. (b) (4) A comprehensive analytical comparability assessment has been performed and the submitted data support the comparability of (b) (4) with (b) (4) for the manufacture of BNT162b2 DS. (b) (4) For DP, the manufacturing process was changed from a Classical process to an Upscale process involving an increase in batch size (capable of accommodating larger RNA input) to meet commercial need. A comparison of available DP batch release data and an in-depth analytical comparability assessment between six representative Classical process DP batches and one Upscale process DP batch support the use of the Upscale process for DP manufacture under emergency use. A more comprehensive comparability assessment encompassing additional lots from multiple DP manufacturing nodes is ongoing and the results will be provided to the EUA upon completion of the study.

Stability studies have been designed to support the use of vaccine under the EUA. All available stability data generated using the BNT162b2 DS and DP lots support the emergency deployment of the Pfizer-BioNTech COVID-19 Vaccine. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of BNT162b2 DS and DP include tests to ensure their identity, purity, quality, and potency. The assays are appropriate and acceptable to be used for the control of DS/DP quality. All analytical procedures used for the release of emergency supply DS and DP have been adequately

qualified. The summaries of the qualification results demonstrate precision, accuracy, sensitivity, specificity, and reproducibility for each evaluated analytical assay, indicating that they are suitable for the intended use.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.
- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also reviewed the inspectional histories of each facility in addition to all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine under an Emergency Use Authorization.

5.5. Clinical Assay Information

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. The Cepheid Xpert Xpress RT-PCR assay is used to assess viral infection of the subjects before vaccination and to confirm COVID-19 cases during study follow-up. The Roche Elecsys Anti-SARS-CoV-2 assay is used to assess serostatus of the subjects before vaccination. Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended use in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

5.6. Inspections of Clinical Study Sites

Bioresearch Monitoring (BIMO) inspections were conducted at six domestic clinical investigator sites participating in the conduct of study protocol C4591001. Based on the preliminary review of the inspection reports, the inspections did not reveal problems impacting the data submitted in support of this EUA.

5.7. EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

6.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

6.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such

as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination. Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection).

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term

effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[12-15] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

6.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) ($\underline{\leq}$2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the Phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically

reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

While not observed in the clinical trials, two anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom, in individuals reported to have prior history of anaphylactic reaction. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time, and the two individuals were not reported to have known history of allergy to specific components of the vaccine. Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis will be further evaluated as part of the pharmacovigilance plan for the vaccine.

6.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Meeting Summary

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on December 10, 2020, to discuss Pfizer's EUA request. The meeting agenda included: an overview by FDA on EUA and considerations specific to COVID-19 vaccines; updates from

CDC on COVID-19 epidemiology, plans for further evaluation of vaccine safety and effectiveness monitoring during use under an EUA, and operational distribution plans; a presentation on conduct of placebo-controlled studies in the event that a vaccine becomes available under EUA; a public comment period; presentations of data from studies of the Pfizer-BioNTech COVID-19 Vaccine by representatives of Pfizer, an FDA presentation of its independent review of the data submitted in support of the EUA request, and a discussion and vote by the VRBPAC.

The VRBPAC was asked to discuss the following points, with no vote:

- Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.
- Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech Vaccine under an EUA.

The committee discussed potential implications of loss of blinded, placebo-controlled follow-up in ongoing trials including how this may impact availability of safety data to support a biologics license application. Some pointed out the importance of long-term safety data for the Pfizer-BioNTech COVID-19 Vaccine as it is made using a technology not used in previously licensed vaccines. In response to the question whether the ongoing Phase 3 study would still be sufficiently powered if eligible placebo recipients would be vaccinated, Pfizer asserted that even with an anticipated loss of placebo-controlled follow-up of 20%, the study would maintain adequate statistical power and would be positioned to accrue additional data on vaccine efficacy, including efficacy against severe disease, as well as safety, although unblinding of the study would reduce interpretability of results. It was pointed out that non-random loss of placebo recipients from the study, as would be expected when unblinded placebo recipients would receive vaccination based on Advisory Committee on Immunization Practices (ACIP) recommendations, would further reduce interpretability of results. There was also discussion of a blinded trial design proposed by Dean Follman, Ph.D. of NIH in which duration of efficacy would be compared in clinical trial participants originally vaccinated with the vaccine to those later administered the vaccine as part of a planned cross-over. Pfizer stated that this design was considered but would present logistical challenges including the need for reconsenting subjects and additional study visits.

The lack of data on how the vaccine impacts asymptomatic infection and viral shedding was also pointed out and that this should be addressed prior to study unblinding. Other committee members were concerned about limited data available in certain subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2 and certain demographic groups.

The committee inquired about information regarding anaphylactoid reactions occurring in 2 individuals vaccinated with the Pfizer-BioNTech vaccine in the UK. Pfizer briefly summarized the available information, i.e., the two cases of anaphylactoid reactions were in individuals with a strong past history of allergic reactions both of whom carried an epinephrine auto injector. These individuals developed symptoms of anaphylactoid reaction shortly after receiving the vaccine. Both recovered after appropriate treatment. FDA referred to its analysis of safety data derived from the ongoing pivotal trial that excluded subjects with allergic reactions to previous vaccine administrations but did not exclude subjects with non-vaccine related allergies. A slight

numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group compared with the placebo group (137 vs. 111). None of these were considered to be serious, and none of these events occurred in the immediate post-vaccination period. FDA noted that the fact sheet and prescribing information for Pfizer-BioNTech COVID-19 vaccine will include information under the contraindications section that the vaccine should not be administered to individuals with known history of a severe allergic reaction to any component of the vaccine. Under the warning section, there will be a statement that 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.

Following this discussion, the VRBPAC was asked to vote on whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

In reference to the voting question, and prior to the committee members casting their votes committee members asked FDA's perspective on use of the vaccine in pregnancy. FDA explained that data from the preclinical developmental and reproductive toxicity study for this product are expected soon. Even though there are insufficient data to inform vaccine-associated risks in pregnancy, there are also no data warranting a contraindication. Some committee members expressed concerns about including adolescents 16 and 17 years of age in the indication for the vaccine because of the limited amount of safety and efficacy data available in this population. Other committee members encouraged authorization of the vaccine under EUA in adolescents because this would support initiating pediatric clinical trials and because benefits would be expected to outweigh any theoretical risks in this population. Inclusion of vaccines against COVID-19 in the pediatric vaccination schedule will ultimately likely be needed to increase the uptake of the vaccine and to reach herd immunity. Pfizer is planning studies in pediatric subjects using an age-stratified step-down approach. Some committee members raised concerns about the small number of severe COVID-19 cases and limited conclusions about the prevention of severe disease based on the study endpoints. FDA pointed out that vaccine development has a long history and that FDA is not aware of an example of any vaccine that is effective against mild disease that is not also effective against severe disease and that even though limited, data for Pfizer-BioNTech COVID-19 Vaccine suggest efficacy against severe disease.

The results of the vote were as follows: Yes = 17, No = 4, Abstain = 1. Thus, the committee voted in favor of a determination that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older.

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 10, 2020 meeting, the review team concludes that:

- As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2. In the planned final primary efficacy analysis of an ongoing randomized, blinded, placebo-controlled Phase 1/2/3 clinical trial, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the larger group of participants with or without prior infection. Efficacy outcomes were consistently robust (≥93%) across demographic subgroups. Secondary and post-hoc efficacy analyses also suggested efficacy against severe COVID-19, efficacy against COVID-19 in the time period between Dose 1 and Dose 2, and against COVID-19 in subjects with evidence of SARS-CoV-2 vaccination prior to vaccination.

- Based on the data summarized in Sections 4 and 5 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2, reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2, and reduction in the risk of confirmed severe COVID-19 any time after Dose 1. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up (including further evaluation of risk of Bell's palsy and allergic reactions following vaccination), risks associated with vaccination of specific populations such as children younger than 16 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, and available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

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10. Appendix A. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, /AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

Exhibit 5

Pfizer-BioNTech: COVID-19 Vaccine EUA Amendment Review Memorandum (May 10, 2021)

Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request) Amendment
Application Number	EUA 27034 (Amendment 132)
Sponsor	Pfizer, Inc., on behalf of BioNTech SE
Submission Date	April 9, 2021
Receipt Date	April 9, 2021
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Principle Discipline Reviewers from the Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Laura Gottschalk, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Lucia Lee, M.D., Clinical reviewer, OVRR/DVRPA Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	May 10, 2021
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine / BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.3 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 12 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBER	Center for Biologics Evaluation and Research
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DVRPA	Division of Vaccines and Related Products Applications
DVT	deep vein thrombosis
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GMR	geometric mean ratio
GMT	geometric mean titer
HHS	Health and Human Services
IND	Investigational New Drug (application to the FDA)
MIS-C	multisystem inflammatory syndrome in children
OVRR	Office of Vaccines Research and Review
PE	pulmonary embolism
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
TTS	thrombosis with thrombocytopenia syndrome
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy

1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of April 30, 2021, has caused more than 155 million cases of COVID-19 and claimed the lives of more than 3.2 million people worldwide. In the United States, more than 32 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 1.5 million cases (4.7%) were among individuals 11 to 17 years of age. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an Emergency Use Authorization (EUA) for a COVID-19 vaccine after determining that certain statutory requirements are met.

On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 Vaccine (also known as BNT162b2, an mRNA vaccine encoding the SARS-CoV-2 spike glycoprotein and administered as a 2-dose regimen 21 days apart) for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. Issuance of the EUA was based on a finding of vaccine efficacy (VE) of 95% compared to placebo against confirmed COVID-19 at least 7 days after completion of the 2-dose vaccination regimen in a study of approximately 44,000 participants, with a highly favorable benefit/risk balance based on assessment of adverse events in a safety population of approximately 38,000 study participants with a median follow-up of 2 months after completion of the vaccination regimen. On April 9, 2021, the Sponsor (Pfizer, on behalf of Pfizer and BioNTech) submitted a request to amend the EUA to include use in individuals 12 through 15 years of age (abbreviated 12-15 years). The EUA amendment request includes safety and effectiveness data from the ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 2,260 participants 12-15 years of age.

Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). Although a specific level of neutralizing antibodies has not been established to correlate with protection, and other aspects of the immune response elicited by the vaccine may also be important, available clinical and non-clinical data support use of neutralizing antibody responses as a clinically relevant immune biomarker for inferring effectiveness through immunobridging in this specific setting. In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race and sex. In the supplemental efficacy analysis, VE after 7 days post Dose 2 was 100% (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0% (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of greater than 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in up to 2.4% of 12-15-year-old BNT162b2 recipients, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. No deaths were observed in this age group during the follow-up period. Serious adverse events, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events among study participants 12-15 years of age that would suggest a causal relationship to BNT162b2 vaccine. Review of longer-term safety data from participants 16 years and older enrolled in the ongoing study and safety surveillance data from use of the vaccine under EUA has not raised any safety concerns aside from a documented incidence of anaphylaxis (occurring primarily among individuals with history of severe allergic reaction to other medications or foods) of 0.46 cases per million doses administered, similar to reported rates of anaphylaxis following licensed preventive vaccines.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of April 30, 2021, has caused more than 155 million cases of COVID-19 and claimed the lives of more than 3.2 million people worldwide. In the United States, more than 32 million cases and 580,012 deaths have been reported to the CDC. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in the December 11, 2020 emergency use authorization (EUA) decision memorandum for the Pfizer-BioNTech COVID-19 vaccine.[1]

Since March 1, 2020, approximately 1.5 million COVID-19 cases in individuals 11 to 17 years of age have been reported to the Centers for Disease Control and Prevention (CDC). [2] Among these cases approximately 9,200 resulted in hospitalization, with more than 600 ICU admissions and more than 200 deaths. It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested.[3,4] Children

and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults.[5,6] However, because adolescents and adults have similar SARS-CoV-2 viral loads in their nasopharynx, adolescents may play a role in community transmission.[7,8] Transmission of SARS-CoV-2 in school settings is limited, and transmission between school staff members is more common than transmission involving students.[9] There is evidence that SARS-CoV-2 transmission is greater in secondary and high schools than elementary schools.[10,11]

As with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions.[12] Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock.[13] Between May 2020 and March 2021, the CDC received reports of 3,185 cases and 36 deaths that met the definition for MIS-C; most cases occurred in children ages 1 to 14 years (median age 9 years), in males (59%), and in children who were reported as Hispanic or Black (64%).[14]

Other impacts of COVID-19 on adolescents include limited access to basic services such as healthcare and child protective services, and social isolation due to disruption of school, sports, and social group gatherings. Published studies have highlighted increases in symptoms of depression, and anxiety[15,16] and increased rates of suicidal ideation and attempts among adolescents during the pandemic.[17]

2.2 Authorized Vaccines and Therapies for COVID-19

Vaccines to prevent COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks. Pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which allows the FDA to authorize unapproved medical products for use in an emergency when certain criteria are met, the FDA has issued EUAs for three COVID-19 vaccines (Table 1) for use in adults (and for the Pfizer-BioNTech COVID-19 vaccine, use in adolescents ages 16-17 years). The two mRNA vaccines authorized in December 2020 (Pfizer and Moderna) were shown to be >90% effective in preventing COVID-19 in adults, including prevention of severe COVID-19.[18,19] However, no vaccine against COVID-19 has been authorized for use in children and adolescents under 16 years of age.

Table 1. COVID-19 Vaccines Authorized for Emergency Use by the FDA

Sponsor	Regimen	Indicated Population	Date of EUA
Pfizer	2 doses 3 weeks apart	Individuals ≥16 years of age	December 11, 2020
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. FDA subsequently issued EUAs for two monoclonal antibody combinations (casirivimab plus imdevimab and bamlanivimab plus etesevimab) for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.[20,21]

2.3 EUA Amendment Request for the Pfizer-BioNTech COVID-19 Vaccine

Pfizer, in partnership with BioNTech SE, has developed a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles. The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) is administered as a series of two 30-µg intramuscular injections spaced 21 days apart. The vaccine is supplied as a multi-dose vial containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for six 0.3 mL doses. The vaccine is preservative free.

Based on the totality of scientific evidence available at the time, the FDA issued an EUA on December 11, 2020 for use of BNT162b2 to prevent COVID-19 in individuals 16 years of age and older.[1] In the planned final primary efficacy analysis of results from a Phase 2/3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants, vaccine efficacy after 7 days post Dose 2 was 95% (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the larger group of participants with or without prior infection. Efficacy outcomes were consistently high (≥93%) across demographic subgroups. Secondary and post hoc efficacy analyses also suggested efficacy against severe COVID-19, efficacy against COVID-19 in the time period between Dose 1 and Dose 2, and against COVID-19 in subjects with evidence of SARS-CoV-2 infection prior to vaccination. Assessment of the known and potential benefits of the vaccine outweighed the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Identified risks included common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions.

As of the date of this review, more than 134 million doses of Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate of 0.46 cases per million doses administered (similar to reported rates of anaphylaxis following licensed preventive vaccines) and occurring primarily in individuals with history of prior severe allergic reactions to other medications or foods. No other safety signals in Pfizer-BioNTech COVID-19 Vaccine recipients 16 years of age and older, including pregnant individuals, have arisen through ongoing active and passive surveillance (see Section 3.3 for additional details). Reported breakthrough cases of COVID-19 among vaccine recipients have been uncommon and have not raised a concern about vaccine-enhanced disease.[22]

On April 9, 2021, Pfizer and BioNTech submitted a request to amend this EUA for the purpose of expanding the use of BNT162b2 to individuals 12 years of age and older. The request is accompanied by clinical trial data evaluating the safety and effectiveness of the vaccine in 2,260 participants 12-15 years of age, which includes a total of 1,131 vaccine recipients, 58.3% of whom had ≥2 months of follow-up after Dose 2. In this age group, vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in adolescents 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE had been demonstrated). Efficacy against COVID-19 disease was also assessed with descriptive analyses in study participants 12-15 years of age.

2.4 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[23]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner. These same requirements apply for this EUA amendment focusing specifically on use in adolescents 12-15 years of age.

2.5 Applicable Guidance for Industry and Regulatory Considerations

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" February 2021, originally issued October 2020).[24] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in adolescents 12-15 years of age. The timing, design, and appropriate endpoints for pediatric studies would be discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent" COVID-19 from June 2020.[25]

Information Needed to Support an EUA Amendment for Use in Adolescents

Effectiveness

Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to an adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same vaccine (including same dose and regimen). The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the

disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric mean titer and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in adolescent vs. adult populations.

Safety

Considering the burden of COVID-19 in the adolescent age group, and the highly favorable benefit/risk balance for the Pfizer vaccine in adults, FDA determined in discussions with Pfizer that a median safety follow-up of at least 2 months among an overall adolescent study population of at least 1,000 vaccine recipients 12-15 years of age, together with longer-term safety data from younger adult study participants, would be sufficient to assess risks in support of an EUA amendment to allow for use of the vaccine in this age group.

3. FDA Review of Clinical Safety and Effectiveness Data

3.1 Overview of Clinical Studies

The EUA amendment request included data from one ongoing clinical study, summarized in Table 2 below. Study C4591001 is a multi-center, multi-national Phase 1/2/3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study. Data from this study were used to support the existing EUA for individuals 16 years of age and older.[1] The focus of this EUA review is the data for participants 12-15 years of age and a comparison group of participants 16-25 years of age. Additionally, safety data from participants 16-55 years of age (13,069 BNT162b2 recipients, 13,095 placebo recipients) with longer safety follow-up and available data from post-authorization safety surveillance were reviewed to assess for any safety concerns not identified during review of the original EUA request.

Table 2: Study C4591001 in Participants 12 Through 15 and 16 Through 25 Years of Age

Study Number/ Countries	Description	BNT162b2 (30 µg) N	Placebo (Saline) N	Study Status
C4591001 USA, Argentina, Brazil, Germany, South Africa, Turkey	Phase 1/2/3, randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Total: 3009 12-15 years: 1134 16-25 years: 1875	Total: 3043 12-15 years: 1130 16-25 years: 1913	Ongoing

N=Number of randomized participants as of March 13, 2021.
Study C4591001 began in April 2020 (first participant, first visit); participants 12-15 years of age: first participant, first visit was October 15, 2020 (implemented according to protocol amendment 7).

3.2 Study C4591001

3.2.1 Design

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. Adolescents were added to the protocol during Phase 3, following a review of safety data in young adult

participants. This resulted in three age strata as follows: 12-15 years, 16-55 years, and >55 years and older.

The protocol-specified evaluation for vaccine effectiveness in participants 12-15 years of age was defined as an immunobridging evaluation comparing SARS-CoV-2 50% neutralizing antibody titers at 1 month after Dose 2 with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated).

Immunogenicity endpoint for adolescents 12 through 15 years of age

- GMR: the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the two age groups (12-15 years and 16-25 years) 1 month after completion of vaccination, in participants without serological or virological evidence of past SARS CoV-2 infection before and during vaccination regimen.
- Immunobridging would be demonstrated upon rejection of the null hypothesis: GMR of neutralizing antibody titers (adolescents to young adults) <0.67-fold, i.e., the lower bound of the 95% CI for the GMR is >0.67.
- Immunobridging data also included a descriptive analysis of the difference in seroresponse rates (adolescents minus young adults) among participants without prior evidence of SARS-CoV-2 infection. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2.

Supplementary to the immunobridging analysis, adolescents were followed for potential cases of COVID-19 to assess VE using the same methods as for participants 16 years of age and older. The primary efficacy endpoint of Study C4591001 was efficacy of the vaccine against laboratory-confirmed COVID-19 in participants without prior SARS-CoV-2 infection. A second primary efficacy endpoint included participants with and without prior SARS CoV-2 infection. COVID case definitions may be found in the review of the EUA for individuals 16 years of age and older.[1] Efficacy against COVID-19 disease was assessed with descriptive analyses in study participants 12-15 years of age.

Per protocol, since December 14, 2020, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo. Participants 12-15 years of age were all enrolled at sites in the U.S. and remain blinded to treatment assignment, except for 23 (2%) participants who received placebo (N=1129) and elected to be unblinded when they turned 16 years of age so they could receive the vaccine under the EUA as allowed for individuals 16 years and older.

Evaluation of safety

All participants 12-15 years of age recorded local reactions, systemic events, and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after the last dose, and serious AEs (SAEs) from Dose 1 to the data cut-off or participant's unblinding date (whichever was earlier), all which were recorded on the case report form. The data cut-off date for this EUA amendment was March 13, 2021.

Potential COVID-19 illnesses and their sequelae were not reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

Analysis populations

Population	Description
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 2 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 dose of vaccine. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.
Reactogenicity subset	All 12-15-year-old participants in the safety population plus the subset of the 16-25-year-old participants in the safety population who had e-diary data reported after vaccination.

Phase 3 clinical endpoints and analyses outlined in this review are provided for the following age groups:

- Adolescents 12-15 years of age: immunobridging, efficacy and safety
- Young adults 16-25 years of age: reference group for immunogenicity, solicited local reactions and systemic AEs, unsolicited AEs (within 30 minutes, non-serious through 30 days after each vaccination), and SAEs through 30 days after each vaccination
- Adults 16-55 years of age: supportive safety data (SAEs and adverse events of special interest (AESIs) from larger group of adult participants with longer-term follow-up.

3.2.2 FDA Assessment of Phase 2/3 Follow-Up Duration for Participants 12 Through 15 Years of Age

Participants 12-15 years of age began enrollment into Phase 3 of Study C4591001 on October 15, 2020 (implemented with protocol amendment 7). As of the March 13, 2021 data cutoff for this EUA amendment, a total of 2,260 adolescents (1,131 in the BNT162b2 group and 1,129 in the placebo group) were enrolled and contributed to the safety population; 57.9% of participants had ≥2 months of follow-up after Dose 2 (Table 3).

Table 3. Follow-up Duration After Dose 2, Participants 12 Through 15 Years of Age, Safety Population

	Vaccine Group (as Administered)		
Length of Follow-up[c]	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.
[a] N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n=number of subjects with the specified characteristic.
[c] Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

Safety comparator group: As of March 13, 2021, a total of 3,770 participants 16-25 years of age (1,867 in the BNT162b2 group and 1,903 in the placebo group) were enrolled and contributed to the safety population, of which 3,622 (96.1%) and 3,292 (87.3%) participants had ≥1 months and ≥2 month of follow-up, respectively, after Dose 2.

3.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (immunogenicity populations), Table 5 (efficacy populations) and Table 6 (safety population). Within each age group, the percentages of participants who discontinued or were lost to follow-up were generally balanced.

For immunogenicity analyses, the Sponsor planned to select a random sample of 280 participants in the BNT162b2 group for each of the two age groups as an immunogenicity subset for immunobridging. Randomization of participants to the immunogenicity subset was conducted through the use of an interactive response technology based on an interactive web-based response to minimize bias. To maintain blinding of the laboratory personnel, 50 participants who had received placebo were randomly selected from each of the two age groups for serology testing. The population for the analysis of the immunogenicity endpoint (Dose 2 evaluable immunogenicity population) included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo group). The majority of exclusions to the immunogenicity analysis population were due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2 (mostly as the result of limited supply of the qualified viral lot at the testing laboratory) and were generally balanced across age and vaccine groups.

Table 4. Disposition of Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Immunogenicity Populations

Disposition	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Randomized[a]	280 (100.0)	280 (100.0)	50 (100.0)	50 (100.0)
Dose 2 all-available immunogenicity population	210 (75.0)	191 (68.2)	36 (72.0)	34 (68.0)
Participants excluded from Dose 2 all-available immunogenicity population	70 (25.0)	89 (31.8)	14 (28.0)	16 (32.0)

Disposition	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Reason for exclusion[b]				
Did not receive 2 vaccinations	1 (0.4)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Dose 2 evaluable immunogenicity population	209 (74.6)	186 (66.4)	36 (72.0)	32 (64.0)
Participants excluded from evaluable immunogenicity population	71 (25.4)	94 (33.6)	14 (28.0)	18 (36.0)
Reason for exclusion[b]				
Randomized but did not meet all eligibility criteria	0	0	0	0
Did not provide informed consent	0	0	0	0
Did not receive 2 doses of the vaccine to which they were randomly assigned	1 (0.4)	0	0	0
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.4)	2 (0.7)	0	2 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Did not have blood collection within 28-42 days after Dose 2	3 (1.1)	16 (5.7)	0	3 (6.0)
Had important protocol deviation(s) as determined by the clinician	0	0	0	1 (2.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table B, page 1.
[a] These values are the denominators for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.
NA=not applicable

Table 5. Disposition of Participants 12 Through 15 Years of Age, Efficacy Populations

Disposition	BNT162b2 n (%)	Placebo n (%)	Total n (%)
Randomized[a]	1134 (100.0)	1130 (100.0)	2264 (100.0)
Dose 1 all-available efficacy population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Participants without evidence of infection before Dose 1	1028 (90.7)	1023 (90.5)	2051 (90.6)
Participants excluded from Dose 1 all-available efficacy population	3 (0.3)	1 (0.1)	4 (0.2)
Reason for exclusion[b]			
Did not receive at least 1 vaccination	3 (0.3)	1 (0.1)	4 (0.2)
Dose 2 all-available efficacy population	1123 (99.0)	1117 (98.8)	2240 (98.9)
Participants without evidence of infection prior to 7 days after Dose 2	1008 (88.9)	983 (87.0)	1991 (87.9)
Participants excluded from Dose 2 all-available efficacy population	11 (1.0)	13 (1.2)	24 (1.1)
Reason for exclusion[b]			
Did not receive 2 vaccinations	10 (0.9)	13 (1.2)	23 (1.0)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Evaluable efficacy population	1119 (98.7)	1110 (98.2)	2229 (98.5)
Subjects without evidence of infection prior to 7 days after Dose 2	1005 (88.6)	978 (86.5)	1983 (87.6)
Participants excluded from evaluable efficacy (7 days) population	15 (1.3)	20 (1.8)	35 (1.5)

Disposition	BNT162b2 n (%)	Placebo n (%)	Total n (%)
Reason for exclusion[b]			
Randomized but did not meet all eligibility criteria	1 (0.1)	0	1 (0.0)
Did not provide informed consent	0	0	0
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-23 days after Dose 1)	14 (1.2)	19 (1.7)	33 (1.5)
Had other important protocol deviations on or prior to 7 days after Dose 2	0	2 (0.2)	2 (0.1)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table C, pages 2-3.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
[a] These values are the denominators for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.

Table 6. Disposition of Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Safety Populations

Treatment Group	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Randomized (N)[a]	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Completed 1 dose	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Completed 2 doses	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Safety population	1131 (99.7)	1867 (99.5)	1129 (99.9)	1903 (95.9)
Reactogenicity subset	1131 (99.7)	537 (28.6)	1129 (99.9)	561 (29.3)
HIV-positive	0	1 (0.05)	0	0
Participants excluded from safety population	3 (0.26)	8 (0.42)	1 (0.08)	10 (0.52)
Reason for exclusion[b]				
Did not receive study vaccination	3 (0.26)	6 (0.32)	1 (0.08)	7 (0.36)
Unreliable data due to lack of PI oversight	0	2 (0.10)	0	3 (0.15)
Completed at least 2 months follow-up after Dose 2[c]	660 (58.4)	1645 (88.1)	648 (57.4)	1647 (86.5)
Completed 1-month after Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continued in the study up to 1-month after Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	7 (0.6)	12 (0.6)	10 (0.9)	36 (1.9)
Discontinued after Dose 2 and before 1-month post-Dose 2 visit	0	1 (0.1)	7 (0.6)	6 (0.3)
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria	3 (0.3)	4 (0.2)	10 (0.9)	26 (1.4)
Withdrawal by subject	0	6 (0.3)	1 (0.1)	1 (0.1)
Pregnancy	0	1 (0.1)	0	3 (0.2)
Adverse event	2 (0.2)	1 (0.1)	0	0
Physician decision	1 (0.1)	0	0	2 (0.1)
Protocol deviation	0	0	1 (0.1)	2 (0.1)
Lost to follow-up	0	0	0	1 (0.1)

Treatment Group	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)
Withdrawn from study before 1-month post-Dose 2 visit	0	45 (2.4)	2 (0.2)	56 (2.9)
Withdrawn after Dose 1 and before Dose 2	0	25 (1.3)	1 (0.1)	34 (1.8)
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit	0	20 (1.1)	1 (0.1)	22 (1.2)
Reason for withdrawal				
Adverse event	0	0	0	1 (0.1)
Death	0	0	0	0
Withdrawal by subject	0	14 (0.7)	0	19 (1.0)
Lost to follow-up	0	29 (1.5)	0	32 (1.7)
Protocol deviation	0	0	1 (0.1)	1 (0.1)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.1)	0
Physician decision	0	0	0	1 (0.1)
Other	0	1 (0.1)	0	2 (0.1)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table D, pages 3-4.
Note: The Human immunodeficiency virus (HIV)-positive subject included in this summary is not included in the analyses of the overall safety objectives. Safety data based on HIV-positive subjects were analyzed separately.
[a] N: denominator used for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.
[c] The numbers in this row are based on subjects who got dose 2 as administered. Duration of follow-up is based on blinded placebo-controlled follow-up period only.
PI=principal investigator

3.2.4 Demographics and Other Baseline Characteristics

The Dose 2 evaluable immunogenicity population included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo group) (Table 7).

The Dose 2 evaluable immunogenicity population of 12-15-year-olds who received BNT162b2 included 49.3% females, 88.0% White, 7.7% African American, 2.4% Asian, and <2% from other racial groups; 10.5% of participants were Hispanic/Latino. The median age was 14 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 21.5% of participants. Geographically, all participants lived in the U.S. For participants 16-25 years of age in the immunogenicity subset, the demographics characteristics were generally similar to those described in the adolescent population, with the exception of comorbidities and obesity, both of which are slightly more prevalent in the young adult age group.

Table 7. Demographics and Other Baseline Characteristics, Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population[a]

Characteristic	12-15 Years BNT162b2 (N=209) n (%)	16-25 Years BNT162b2 (N=186) n (%)	12-15 Years Placebo (N=36) n (%)	16-25 Years Placebo (N=32) n (%)
Sex: Female	103 (49.3)	94 (50.5)	15 (41.7)	18 (56.3)
Sex: Male	106 (50.7)	92 (49.5)	21 (58.3)	14 (43.8)
Age: Mean years (SD)	13.5 (1.12)	20.6 (3.09)	13.4 (1.17)	20.3 (3.05)
Age: Median (years)	14.0	21.0	13.0	19.5

Characteristic	12-15 Years BNT162b2 (N=209) n (%)	16-25 Years BNT162b2 (N=186) n (%)	12-15 Years Placebo (N=36) n (%)	16-25 Years Placebo (N=32) n (%)
Race: American Indian or Alaska Native	1 (0.5)	3 (1.6)	0	1 (3.1)
Race: Asian	5 (2.4)	10 (5.4)	1 (2.8)	1 (3.1)
Race: Black or African American	16 (7.7)	15 (8.1)	3 (8.3)	2 (6.3)
Race: Native Hawaiian or other Pacific Islander	0	3 (1.6)	0	0
Race: White	184 (88.0)	147 (79.0)	31 (86.1)	28 (87.5)
Race: Multiracial	3 (1.4)	6 (3.2)	1 (2.8)	0
Race: Not reported	0	2 (1.1)	0	0
Ethnicity: Hispanic or Latino	22 (10.5)	31 (16.7)	2 (5.6)	7 (21.9)
Ethnicity: Not Hispanic or Latino	187 (89.5)	154 (82.8)	34 (94.4)	25 (78.1)
Ethnicity: Not reported	0	1 (0.5)	0	0
Obese[b]: Yes	24 (11.5)	43 (23.1)	3 (8.3)	4 (12.5)
Obese: No	185 (88.5)	143 (76.9)	33 (91.7)	28 (87.5)
Comorbidities[c]: Yes	45 (21.5)	56 (30.1)	7 (19.4)	9 (28.1)
Comorbidities: No	164 (78.5)	130 (69.9)	29 (80.6)	23 (71.9)
Baseline evidence of prior SARS-CoV-2 infection: Negative	194 (92.8)	178 (95.7)	33 (91.7)	31 (96.9)
Baseline evidence of prior SARS-CoV-2 infection: Positive	10 (4.8)	8 (4.3)	2 (5.6)	1 (3.1)
Baseline evidence of prior SARS-CoV-2 infection: Unknown	5 (2.4)	0	1 (2.8)	0
Region: North America	209 (100.0)	186 (100.0)	36 (100.0)	32 (100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table E, page 4-5.
[a] All elig ble randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
[b] Obese is defined as BMI ≥30 kg/m2 (≥16 years of age) or BMI ≥95th percentile (12-15 years of age).
[c] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone.
NA=not applicable

The demographic characteristics of the evaluable efficacy population in participants 12-15 years of age for the VE analyses (N=1005 vaccine group, N=978 placebo group) are similar to the baseline characteristics of the Dose 1 all-available efficacy population.

The Dose 1 all-available efficacy population of 12-15-year-olds (BNT162b2 n=1,131, placebo n=1,129) were the same individuals as the 12-15-year-olds as in the safety population (Table 8).

Safety population: Among participants 12-15 years of age, the median age was 14 years, and all participants lived in the U.S. Among participants 16-25 years of age, the median age was 18 years in the BNT162b2 group and 19 years in the placebo group; 81.2% and 77.4% participants, respectively, lived in the U.S.

Table 8. Demographics and Other Baseline Characteristics, Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age (Reactogenicity Subset), Safety Populations[a]

Characteristic	12-15 Years BNT162b2 (N=1131) n (%)	16-25 Years BNT162b2 (N=537) n (%)	12-15 Years Placebo (N=1129) n (%)	16-25 Years Placebo (N=561) n (%)
Sex: Female	564 (49.9)	282 (52.5)	544 (48.2)	292 (52.0)
Sex: Male	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)

Characteristic	12-15 Years BNT162b2 (N=1131) n (%)	16-25 Years BNT162b2 (N=537) n (%)	12-15 Years Placebo (N=1129) n (%)	16-25 Years Placebo (N=561) n (%)
Age: Mean years (SD)	13.6 (1.11)	19.4 (3.26)	13.6 (1.11)	19.6 (3.33)
Age: Median (years)	14.0	18.0	14.0	19.0
Race: American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Race: Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Race: Black or African American	52(4.6)	47 (8.8)	57 (5.0)	50 (8.9)
Race: Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Race: White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Race: Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Race: Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Race: Other	0	0	0	0
Ethnicity: Hispanic or Latino	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Ethnicity: Not Hispanic or Latino	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Ethnicity: Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Obese: Yes	143 (12.6)	80 (14.9)	128 (11.3)	101 (18.0)
Obese: No	988 (87.4)	457 (85.1)	1001 (88.7)	460 (82.0)
Comorbidities[b]: Yes	248 (21.9)	126 (23.5)	240 (21.3)	144 (25.7)
Comorbidities: No	883 (78.1)	411 (76.5)	889 (78.7)	417 (74.3)
Baseline evidence of prior SARS-CoV-2 infection: Negative	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Baseline evidence of prior SARS-CoV-2 infection: Positive	46 (4.1)	30 (5.6)	47 (4.2)	34 (6.1)
Baseline evidence of prior SARS-CoV-2 infection: Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)
Region: North America	1131 (100.0)	436 (81.2)	1129 (100.0)	434 (77.4)
Country: Argentina	0	20 (3.7)	0	28 (5.0)
Country: Brazil	0	24 (4.5)	0	19 (3.4)
Country: Germany	0	11 (2.0)	0	20 (3.6)
Country: South Africa	0	34 (6.3)	0	45 (8.0)
Country: Turkey	0	12 (2.2)	0	15 (2.7)

Sources: EUA 27034.132, eua-amend-12-15-years.pdf, Table 5, page 23 and c4591001--12-15-tables-figures.docx, Table P, page 7-9.
[a] All randomized participants who receive at least 1 dose of the study intervention.
[b] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age].[b] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone.(BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age].

3.2.5 Vaccine Effectiveness

Immunogenicity

The immune response to BNT162b2 in adolescents 12-15 years of age was noninferior to that observed in young adults 16-25 years of age, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2 in participants without prior evidence of SARS-CoV-2 infection. The geometric mean titer (GMT) ratio of adolescent to young adult neutralizing antibody titers was

1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5-fold non-inferiority criterion (i.e., lower bound of the 2-sided 95% CI for GMR >0.67).

Table 9. Geometric Mean SARS-CoV-2 Neutralizing Titers (NT50) 1 Month After BNT162b2 Dose 2 in Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population

Study Group	12-15 Years N=190 GMT (95% CI)	16-25 Years N=170 GMT (95% CI)	GMT Ratio [12-15 Years/ 16-25 Years] (95% CI)	Met Predefined Success Criterion[a]
BNT162b2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 85.
[a] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
N=Number of participants with valid and determinate assay results for the specified assay at 1 month after Dose 2.
GMT=geometric mean titer

The GMR of SARS CoV-2 neutralizing titers one month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to evaluate by protocol-specified methods.

Table 10. Subgroup Analyses of Geometric Mean SARS-CoV-2 Neutralizing Titers (NT 50) One Month After BNT162b2 Dose 2 in Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Dose 2 All-Available Immunogenicity Population

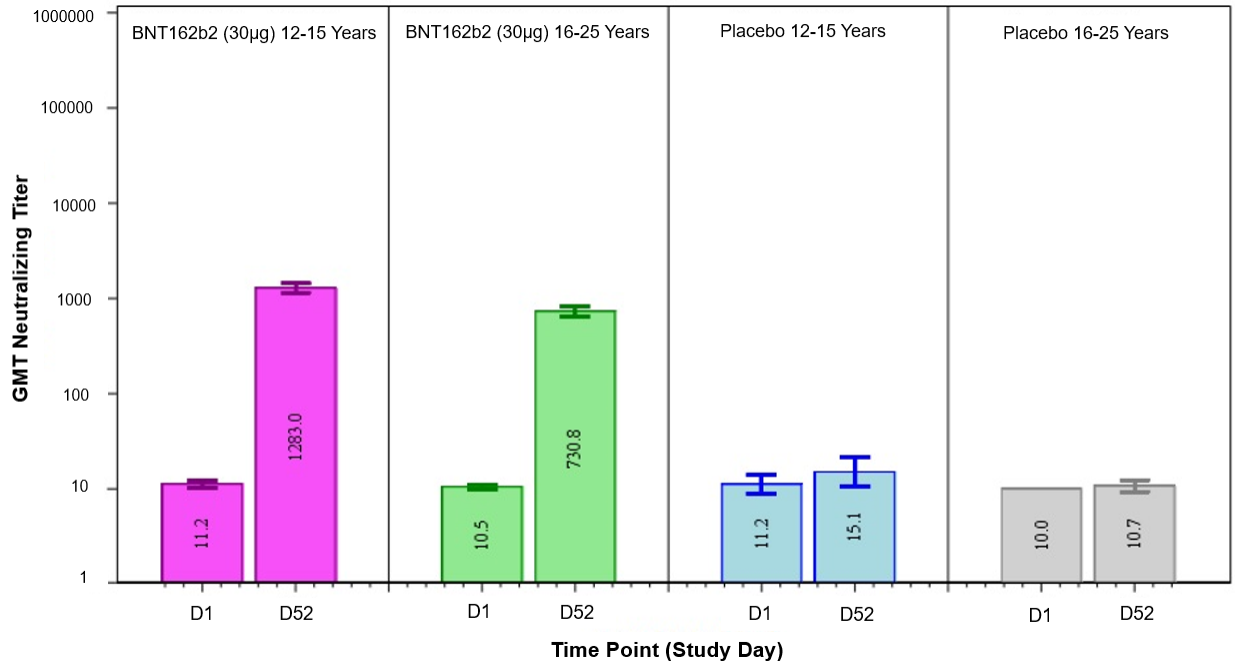
Subgroup	12-15 Years N, GMT (95% CI)	16-25 Years N, GMT (95% CI)	GMT Ratio [definition] (95% CI)
Comorbid condition[a]: Yes	45, 1460.3 (1218.2, 1750.5)	56, 712.4 (546.0,929.5)	2.05 (1.49, 2.82)
Comorbid condition: No	163, 1239.7 (1075.2, 1429.3)	134, 732.1 (641.6, 835.5)	1.69 (1.40, 2.05)
Obese: Yes	24, 1596.9 (1233.2, 2067.8)	43, 802.4 (613.5, 1049.4)	1.99 (1.33, 2.97)
Obese: No	184, 1248.4 (1097.1, 1420.5)	147, 705.4 (615.9, 807.9)	1.77 (1.47, 2.14)
Baseline SARS-CoV-2: Positive	10, 2342.2 (1308.7, 4191.8)	8, 1439.2 (727.1, 2848.7)	1.63 (0.72, 3.69)
Baseline SARS-CoV-2: Negative	193, 1240.9 (1098.7, 1401.5)	182, 704.7 (624.1, 795.9)	1.76 (1.48, 2.09)
Baseline SARS-CoV-2: Unknown	5, 1458.7 (479.2, 4440.9)	0, NE (NE, NE)	NE
Sex: Female	102, 1315.5 (1123.4, 1540.3)	98, 793.4 (665.9, 945.2)	1.66 (1.31, 2.09)
Sex: Male	106, 1255.2 (1051.3, 1498.5)	92, 661.0 (560.2, 780.0)	1.90 (1.49, 2.42)
Ethnicity: Hispanic or Latino	22, 1276.2 (917.9, 1774.4)	31, 662.4 (472.3, 928.9)	1.93 (1.20, 3.11)
Ethnicity: Not Hispanic or Latino	186, 1285.4 (1132.0, 1459.4)	158, 743.4 (652.9, 846.4)	1.73 (1.44, 2.07)
Ethnicity: Not reported	0, NE (NE, NE)	1,318.0 (NE, NE)	NE
Race: American Indian or Alaska Native	1, 908.0 (NE, NE)	3, 1130.7 (13.7, 93052.6)	0.80 (NE, NE)
Race: Asian	5, 1338.9 (625.6, 2865.8)	10, 649.6 (408.5, 1033.1)	2.06 (0.97, 4.38)

Subgroup	12-15 Years N, GMT (95% CI)	16-25 Years N, GMT (95% CI)	GMT Ratio [definition] (95% CI)
Race: Black or African American	16, 1377.3 (963.1, 1969.4)	15, 803.4 (409.7, 1575.8)	1.71 (0.82, 3.59)
Race: Native Hawaiian or Other Pacific Islander	0, NE (NE, NE)	4, 756.5 (184.9, 3094.1)	NE
Race: White	183, 1286.2 (1129.4, 1464.9)	150, 720.4 (633.2, 819.7)	1.79 (1.48, 2.15)
Race: Multiracial	3, 848.4 (224.8, 3202.1)	6, 741.5 (304.5, 1805.7)	1.14 (0.31, 4.16)
Race: Not reported	0, NE (NE, NE)	2, 486.7 (2.2, 108697.3)	NE

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table H, pages 6-8.
[a] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age]).
N=Number of subjects with valid and determinate assay results for the specified assay at 1 month after Dose 2.
GMT=geometric mean titer, NE=not estimable

The baseline SARS-CoV-2 neutralizing antibody GMTs obtained prior to vaccination were equally low in both of the age groups, with an observed increase in GMTs one month after Dose 2 in vaccine participants (Figure 1).

Figure 1. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population



Source: EUA 27034, amendment 132, Figure 5; eua-amend-12-15-years.pdf, page 89.
D=day, GMT=geometric mean titer, NT50=50% neutralizing titer
Note: Number within each bar denotes geometric mean titer.

Seroresponse rates among participants without prior evidence of SARS-CoV-2 infection are displayed in Table 11, below. A ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2 was seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Of the 3 adolescents

for whom laboratory results did not meet the seroresponse definition, 2 of them failed to respond, with negative neutralizing antibody titers before and after vaccination. The other adolescent had a baseline positive neutralizing antibody titer of 776 despite having a baseline negative N-binding antibody titer and had a titer of 962 at 1 month after Dose 2, which was not an increase of at least 4-fold as required to meet the seroresponse definition.

Table 11. Seroconversion Rates – NT50 – 1 Month After BNT162b2 Dose 2, Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population

Study Group	12-15 Years N=143 n, SCR (%) (95% CI)	16-25 Years N=124 n, SCR (%) (95% CI)	Difference in Seroconversion Rates[a] (95% CI)
BNT162b2	140 (97.9) (94.0, 99.6)	124 (100.0) (97.1, 100.0)	-2.1 (-6.0, 0.9)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 86.
[a] Seroconversion is defined as achieving a ≥4-fold rise from baseline (before vaccination).
N=number of participants with valid and determinate assay results for the specified assay both before vaccination and at 1 month after Dose 2.
n=number of participants with ≥4-fold rise from before vaccination to 1 month after Dose 2
SCR=seroconversion rate

Clinical disease endpoint efficacy

The protocol-specified final analysis of efficacy was completed with a data cutoff date of November 14, 2020. At that time, only 100 participants 12-15 years of age (49 in the BNT162b2 group and 51 in the placebo group) had enrolled in the study, and there were no confirmed COVID-19 cases in this age group. Therefore, additional descriptive analyses of VE in adolescents 12-15 years of age were conducted with all cases accrued during blinded follow-up to a data cutoff date of March 13, 2021.

For the first efficacy endpoint in participants 12-15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0%. The case split was 0 COVID-19 cases in the BNT162b2 group compared to 16 COVID-19 cases in the placebo group (Table 12). The 95% confidence interval for the VE was 75.3% to 100.0%.

Table 12. Vaccine Efficacy, Participants 12 Through 15 Years of Age Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population

Endpoint	BNT162b2 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]
First COVID-19 occurrence from 7 days after Dose 2 in subjects without evidence of prior SARS-CoV-2 infection	0, 0.154 (1001)	16, 0.147 (972)	100.0 (75.3, 100.0)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 18, page 76.
[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 VE based on the Clopper-Pearson method adjusted to the surveillance time.

For the second efficacy endpoint in participants 12-15 years of age with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was also 100.0%, with 0 and 18 cases in the BNT162b2 and placebo groups, respectively. The 95% confidence interval for the VE was 78.1% to 100.0%.

Subgroup analyses of vaccine efficacy

The demographics of the participants with confirmed COVID-19 cases contributing to the efficacy analysis are displayed below in Table 13. All confirmed COVID-19 cases occurred in the placebo group in participants who had negative baseline SARS-CoV-2 prior infection status and who identified as White.

Table 13. Demographic Characteristics, Participants 12 Through 15 Years of Age With Protocol-Defined COVID-19 (With or Without Evidence of Infection Prior to 7 Days After Dose 2)

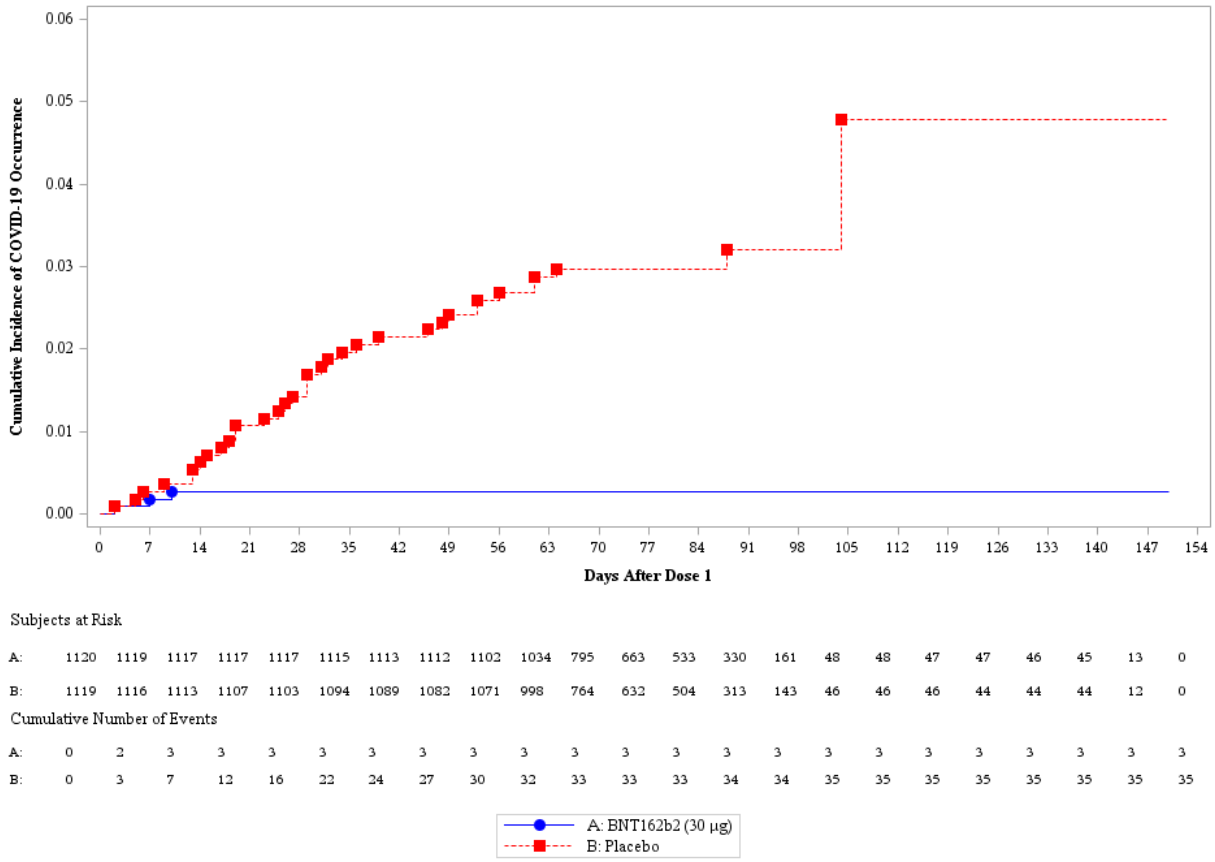
Characteristic	BNT162b2 N=0 n (%)	Placebo N=18 n (%)
Sex: Female	0	6 (33.3)
Sex: Male	0	12 (66.7)
Age at vaccination: Mean years (SD)	0	13.9 (1.16)
Age at vaccination: Median (years)	0	14.0
Race: American Indian or Alaska Native	0	0
Race: Asian	0	0
Race: Black or African American	0	0
Race: Native Hawaiian or Other Pacific Islander	0	0
Race: White	0	18 (100.0)
Race: Multiracial	0	0
Ethnicity: Hispanic or Latino	0	5 (27.8)
Ethnicity: Not Hispanic or Latino	0	13 (72.2)
Comorbidities[a]: Yes	0	7 (38.9)
Comorbidities: No	0	11 (61.1)
Comorbidity: Obesity	0	4 (22.2)
Baseline SARS-CoV-2 Status: Negative	0	18 (100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables L and M1, pages 12-14.
[a] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m^2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age]).

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1 (Figure 2), there are similar numbers of COVID-19 cases in the BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months following the second dose, there does not appear to be waning protection in the BNT162b2 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population



Source: EUA 27034, amendment 132; c4591001-508-compliant-tables-12-15.pdf, page 15.

Severe COVID-19 cases

There were no reports of severe COVID-19 cases (and no cases of MIS-C) in participants 12-15 years of age.

Additional efficacy analyses

Additional analyses of the efficacy endpoint were conducted to evaluate the all-available efficacy population of participants 12-15 years of age, regardless of evidence of prior infection from Dose 1 through 7 days after Dose 2 (Table 14).

Table 14. Primary Efficacy Endpoint, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=1131 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1129 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence after Dose 1	3 0.257 (1120)	35 0.250 (1119)	91.6 (73.5, 98.4)
After Dose 1 to before Dose 2	3	12	75.0 (7.4, 95.5)
Dose 2 to 7 days after Dose 2	0	5	100.0 (-9.1, 100.0)
≥7 Days after Dose 2	0	18	100.0 (77.3, 100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables N, pages 16.
[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 Dose 1 to the end of the surveillance period.
[d] n2=number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper-Pearson method (adjusted for surveillance time for overall row).

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 91.6%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, the point estimate is lower than efficacy post-Dose 2, and post-Dose 1 data do not provide information about longer term protection beyond 21 days after a single dose.

3.2.6 Safety

Overview of adverse events

Table 15 summarizes adverse events in the safety population. All participants 12-15 years of age in the safety population were also enrolled in the reactogenicity subset. Of 3,788 participants 16-25 years of age, 29% were included in the reactogenicity subset.

Table 15. Safety Overview, Participants 12 Through 15 Years and Participants 16 Through 25 Years of Age

Event	12-15 Years BNT162b2 n/N (%)	12-15 Years Placebo n/N (%)	16-25 Years BNT162b2 n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination[a]			
Dose 1	0/1131 (0.0)	4/1129 (0.4)	11/1866 (0.6)
Dose 2	2/1124 (0.2)	3/1117 (0.3)	7/1818 (0.4)
Solicited injection site reaction within 7 days[a]			
Dose 1	976/1127 (86.6)	271/1127 (24.0)	445/531 (83.8)
Dose 2	872/1097 (79.5)	198/1078 (18.4)	381/488 (78.1)
Solicited systemic AE within 7 days[a]			
Dose 1	877/1127 (77.8)	636/1127 (56.4)	403/531 (75.9)
Dose 2	904/1097 (82.4)	439/1078 (40.7)	396/488 (81.1)
From Dose 1 through 1 month after Dose 2[b]			
Unsolicited non-serious AE	64/1131 (5.7)	66/1129 (5.8)	521/1866 (27.9)
SAE	4/1131 (0.4)	1/1129 (0.1)	6/1866 (0.3)

Event	12-15 Years BNT162b2 n/N (%)	12-15 Years Placebo n/N (%)	16-25 Years BNT162b2 n/N (%)
From Dose 1 to cutoff date or participant blinding (whichever is earlier)[b]			
SAE	5/1131 (0.4)	2/1129 (0.2)	8/1866 (0.4)
Withdrawal due to AEs	2/1131(0.2)	0	2/1866 (0.1)
Deaths	0	0	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables Q and Q.1, pages 17-18.
n: number of participants reporting the adverse event.
[a] N: number of participants in the specified age group in the reactogenicity subset of the safety population with data available for the adverse event.
[b] N: number of participants in the specified age group in the safety population.

Immediate AEs

12-15-year-olds
After Dose 1:

- No BNT162b2 recipients reported an immediate AE
- Four (0.4%) placebo recipients reported a total of 5 AEs: injection site pain [n=3], headache [n=1], dizziness [n=1]

After Dose 2:

- Two (0.2%) BNT162b2 recipients reported a total of 2 AEs: injection site pain [n=1], dizziness [n=1]
- Three (0.3%) placebo recipients reported a total of 4 AEs: injection site pain [n=1], fatigue [n=1], chills [n=1], rash [n=1]

The immediate AEs described above were consistent with solicited reactions/events reported among participants in the reactogenicity subset during the first 7 days following vaccination.

One (1) BNT162b2 recipient and 1 placebo recipient reported symptoms on the day of vaccination that were consistent with pre-syncope (after BNT162b2 Dose 2 and after placebo dose 1, respectively). Vasovagal reactions are not uncommon in adolescents following vaccinations and other medical procedures involving needlesticks; the Prescribing Information and Fact Sheet for Healthcare Providers for the authorized Pfizer-BioNTech COVID-19 Vaccine include a warning about measures to avoid injury following vasovagal/syncopal episodes in the immediate post-vaccination period.

Comparator group of 16-25-year-olds: Among the BNT162b2 and placebo groups, the immediate AEs after Dose 1 and after Dose 2 were 0.4%-0.6%, and mostly due to injection site pain.

Anaphylaxis: There were no reports of anaphylaxis in the 12-15-year or 16-25-year age groups through the cutoff date of March 13, 2021.

Solicited local reactions and systemic adverse events

Solicited local reactions

For BNT162b2 recipients in both age groups, injection site pain was the most frequent solicited local adverse reaction. The median onset for all solicited local reactions after either BNT162b2 dose was Day 1 (day of vaccination) to Day 3, and the median duration was 1-3 days. Local

reactions occurred more frequently after Dose 1 than after Dose 2. Injection site reactions following both doses were mostly mild to moderate, and frequencies of severe local reactions were lower in participants 12-15 years of age than in participants 16-25 years of age.

Among 12-15-year-olds, injection site reactions were more frequent in the BNT162b2 group than in the placebo group.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset[a]

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Pain at the injection site[b]						
Any[d]	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)	443 (83.4)	378 (77.5)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)	204 (38.4)	202 (41.4)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)	227 (42.7)	169 (34.6)
Severe	11 (1.0)	0	7 (0.6)	0	12 (2.3)	7 (1.4)
Redness[c]						
Any[d]	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)	34 (6.4)	28 (5.7)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)	25 (4.7)	18 (3.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)	7 (1.3)	9 (1.8)
Severe	1 (0.1)	0	0	0	2 (0.4)	1 (0.2)
Swelling[c]						
Any[d]	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)	44 (8.3)	33 (6.8)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)	31 (5.8)	23 (4.7)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)	12 (2.3)	10 (2.0)
Severe	0	0	0	0	1 (0.2)	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables R and R.1, pages 18-19.
%:n/N. n=number of participants in the specified age group with the specified reaction. N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[c] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
[d] Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

Solicited systemic AEs

Among BNT162b2 recipients in both age groups, fatigue and headache were most common. The median onset of systemic events after either BNT162b2 dose occurred on Day 1 to Day 4, with resolution after a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days. Solicited systemic AEs following both doses were mostly mild to moderate, and frequencies of severe systemic AEs, muscle pain, and joint pain were lower in participants 12-15 years of age than in those 16-25 years of age.

Within each age group, the frequency and severity of systemic AEs was higher after BNT162b2 Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar for both doses.

Among 12-15-year-olds, systemic AEs were more frequently reported in BNT162b2 recipients than in the placebo group.

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset[a]

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Fever						
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)	39 (7.3)	84 (17.2)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)	24 (4.5)	45 (9.2)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)	12 (2.3)	32 (6.6)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)	3 (0.6)	7 (1.4)
>40.0°C	1 (0.1)	0	0	0	0	0
Fatigue[b]						
Any[e]	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)	318 (59.9)	320 (65.6)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)	134 (25.2)	98 (20.1)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)	173 (32.6)	199 (40.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)	11 (2.1)	23 (4.7)
Headache[b]						
Any[e]	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)	286 (53.9)	297 (60.9)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)	151 (28.4)	119 (24.4)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)	124 (23.4)	157 (32.2)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)	11 (2.1)	21 (4.3)
Chills[b]						
Any[e]	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)	133 (25.0)	195 (40.0)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)	91 (17.1)	82 (16.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)	37 (7.0)	101 (20.7)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0	5 (0.9)	12 (2.5)
Vomiting[c]						
Any[e]	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)	9 (1.7)	13 (2.7)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)	9 (1.7)	10 (2.0)
Moderate	0	2 (0.2)	4 (0.4)	1 (0.1)	0	3 (0.6)
Severe	1 (0.1)	0	0	0	0	0
Diarrhea[d]						
Any[e]	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)	57 (10.7)	39 (8.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)	50 (9.4)	32 (6.6)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)	7 (1.3)	5 (1.0)
Severe	0	0	0	0	0	2 (0.4)
New or worsened muscle pain[a]						
Any[e]	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)	143 (26.9)	199 (40.8)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)	67 (12.6)	93 (19.1)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)	71 (13.4)	97 (19.9)
Severe	2 (0.2)	0	6 (0.5)	2 (0.2)	5 (0.9)	9 (1.8)
New or worsened joint pain[a]						
Any[e]	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)	70 (13.2)	107 (21.9)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)	38 (7.2)	49 (10.0)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)	29 (5.5)	54 (11.1)
Severe	1 (0.1)	0	4 (0.4)	0	3 (0.6)	4 (0.8)

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Use of antipyretic or pain medication[f]	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)	167 (31.5)	223 (45.7)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables S and S.1, pages 20-22.
%:n/N. n=number of participants in the specified age group with the specified characteristic.
N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[c] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[d] 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.
[e] Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
[f] Severity was not collected for use of antipyretic or pain medication.

Subgroup analyses

Among 12-15-year-old BNT162b2 recipients, the frequencies of solicited local reactions and systemic AEs were generally similar among males and females.

Ethnicity: After Dose 2, Hispanic/Latino vaccine recipients reported notably lower rates for certain systemic AEs and higher rates for certain local reactions than non-Hispanic/non-Latino vaccine recipients.

- any fever: 9.4% (95%CI 4.9, 15.8) vs. 21.0% (95% CI 18.5, 23.7)
- any headache: 51.6% (95%CI 42.6, 60.5) vs. 66.3% (95% CI 63.2, 69.3)

These findings were accompanied by less antipyretic use after Dose 2 among Hispanic/Latino vaccine recipients compared with non-Hispanic/Latino vaccine recipients.

- any injection site swelling: 11.4% (95%CI 6.5, 18.0) vs. 4.7% (95% CI 3.4, 6.2)
- any injection site pain: 89.4% (95%CI 82.8, 94.1) vs. 79.1% (95% CI 76.4, 81.6)

Reactogenicity after Dose 1 was similar among Hispanic/Latino and non-Hispanic/non-Latino vaccine recipients.

The frequencies of solicited local reactions and systemic AEs were generally similar by race. While the proportions of African American, Asian and other racial groups in the study were reflective of the general distribution in the US population, the numbers of BNT162b2 recipients in these racial groups are too small (total n=157) to make definitive conclusions.

Reactogenicity in BNT162b2 recipients who were SARS-CoV-2 positive prior to Dose 1 (n=46) was similar to the overall population of vaccine recipients, but the number of subjects were too small to make definitive conclusions.

Unsolicited (non-serious and serious) AEs

Non-serious unsolicited AEs

Dose 1 through 1 month after Dose 2

Overall, among 12-15-year-olds, approximately 5.8% of participants in each treatment group (BNT162b2 and placebo) reported at least 1 non-serious AE from Dose 1 through 1 month after Dose 2 in ongoing follow-up. Differences in frequencies of AEs between the vaccine and placebo groups were notable for fever with onset within 7 days after vaccination and lymphadenopathy.

Reactogenicity

12-15-year-olds: 5 (0.4%) BNT162b2 recipients and 0 placebo recipients reported fever. AEs in the Medical Dictionary for Regulatory Activities System Organ Class (SOC) *General disorders and administration site conditions* were most frequently reported of all non-serious, unsolicited AEs in the BNT162b2 and placebo groups, of which injection site pain (0.6% BNT162b2, 0.6% placebo) and fatigue (0.6% BNT162b2, 0.4% placebo) were most common.

Comparator group of 16-25-year-olds (safety population): Approximately 50% of 16-25-year-olds were included in the reactogenicity subset, compared to 12-15-year-olds, who were all enrolled in the reactogenicity subset. Therefore, overall frequencies of reported unsolicited non-serious AEs in BNT162b2 recipients (27.9%) compared to placebo recipients (12.7%) were higher among 16-25-year-olds than 12-15-years-olds, primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination and were consistent with adverse reactions/events solicited among participants in the reactogenicity subset.

Lymphadenopathy

12-15-year-olds: 7 (0.6%) BNT162b2 recipients and 1 (0.1%) placebo recipient reported lymphadenopathy; all of the events occurred within 2-10 days after study intervention, were located mainly in the arm/neck (axillary, cervical, supraclavicular lymph nodes), and were assessed as related to the study product by the investigator. In approximately 50% of participants, lymphadenopathy resolved within 1-10 days; in the remaining participants, the AE was ongoing at the time of data cutoff. Three additional reports of lymphadenopathy (2 BNT162b2 recipients and 1 placebo recipient) were assessed as unrelated by the study investigator due to onset ≥28 days after Dose 2 in the 2 BNT162b2 recipients and concurrent infectious mononucleosis in the placebo recipient. FDA agrees with the investigator's assessments.

Comparator group of 16-25-year-olds (safety population)*:* 7 (0.6%) BNT162b2 recipients reported lymphadenopathy, all plausibly related to vaccination, and no placebo recipients.

Hypersensitivity Reactions

12-15-year-olds: 6 BNT162b2 (0.53%) and 10 (0.89%) placebo recipients reported hypersensitivity-associated AEs, which were most frequently AEs included in the SOC *Skin and subcutaneous tissue disorders*; urticaria was most common in both study groups.

Comparator group of 16-25-year-olds (reactogenicity subset)*:* 6 BNT162b2 (1.12%) and 0 (0%) placebo recipients reported hypersensitivity-associated AEs, which were most frequently AEs included in the SOC *Skin and subcutaneous tissue disorders*; events categorized as 'rash' were most common.

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)

12-15-year-olds: Other than lymphadenopathy, reactogenicity and hypersensitivity events reported from Dose 1 through 1 month after Dose 2, there were no other notable patterns between treatment groups for specific categories (SOC and Preferred Term (PT)) of non-serious adverse events, including Bell's palsy, facial paralysis/paresis, other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Comparator group of 16-25-year-olds (safety population): Unsolicited, non-serious AEs reported by 16-25-year-olds (from Dose 1 to the participant's unblinding date) are described in the Supplemental Safety Data section of this memo because their duration of safety follow-up was longer and thus more similar to that of the adult population than to that of 12-15-year-olds.

SAEs

Dose 1 through 1 month after Dose 2

12-15-year-olds: SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of BNT162b2 recipients and 0.1% of placebo recipients. A total of 5 SAEs were reported by 5 recipients (4 BNT162b2, 1 placebo), all who had no history of prior SARS-CoV-2 infection (SARS-CoV-2 negative at baseline).

BNT162b2:

- 3 participants, all with pre-existing anxiety and depression, were hospitalized for medical management of depression exacerbation that started 7 days after Dose 1, 1 day after Dose 2, and 15 days after Dose 1, respectively. All 3 participants reported treatment with a selective serotonin reuptake inhibitor (SSRI) that began within 1-2 months prior to vaccination. Worsening suicidal ideas with initial SSRI treatment in adolescents is a recognized risk and provides a reasonable alternative explanation for depression exacerbation in these BNT162b2 recipients.

- One participant experienced an SAE reported as generalized neuralgia, and also reported 3 concurrent non-serious AEs (abdominal pain, abscess, gastritis) and 1 concurrent SAE (constipation) within the same week. The participant was eventually diagnosed with functional abdominal pain. The event was reported as ongoing at the time of the cutoff date.

Placebo:

- One participant was hospitalized for appendicitis 19 days after Dose 2. The event resolved after 2 days and the participant continued in the study.

Comparator group of 16-25-year-olds (safety population): SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.3% of BNT162b2 recipients and 0.2% of placebo recipients. Six BNT162b2 recipients reported a total of 7 SAEs: concurrent

choledocholithiasis (1) and pancreatitis (1) in the same recipient; abdominal pain (1), appendicitis (1), deep vein thrombosis (DVT) (1), facial fracture (1), and osteochondritis (1). The DVT in the leg, which the study investigator attributed to a recent ankle fracture, occurred 19 days after BNT162b2 Dose 2. Clinical laboratory results were not provided. The event was ongoing at the time of the cut-off date. All SAEs in BNT162b2 recipients were considered unrelated to vaccination by the study investigator. No further information was provided by the Sponsor.

Four placebo recipients reported 4 SAEs: appendicitis (1), inguinal hernia (1), flail chest (associated with a motor vehicle accident) (1), and incomplete spontaneous abortion (1).

1 month after Dose 2 to data cutoff date or participant's unblinding date (whichever was earlier)

12-15-year-olds: A total of 3 SAEs from 1 month after Dose 2 in ongoing follow-up were reported in 3 recipients (2 BNT162b2, 1 placebo). All SAEs in BNT162b2 recipients were considered unrelated to vaccination by the study investigator and by FDA.

BNT162b2:

- 1 participant with constipation was diagnosed with functional abdominal pain after an extensive work-up; the participant also developed generalized neuralgia beginning 1 day after Dose 2 (described above).
- 1 participant with a long-standing history of ADHD and recent anxiety and depression diagnoses (4 months and 10 days prior to enrollment, respectively) was hospitalized for suicidal ideation 40 days after Dose 2. The event was ongoing at the time of the data cut-off date, but per the narrative provided by the Sponsor the event was assessed as resolved on March 15, 2021. The study investigator attributed the participant's symptoms to psychosocial issues expressed by the participant as the cause of her exacerbation.

Placebo:

- One participant was hospitalized for appendicitis 63 days after the Dose 2 of placebo. Symptoms were ongoing as of the data cutoff date.

Comparator group of 16-25-year-olds (safety population): Non-fatal SAEs described for 16-25-year-olds (from 1 month after Dose 2 to data cutoff or the participant's unblinding date, whichever was earlier) are described in the Supplemental Safety Data section of this memo because their duration of safety follow-up was longer and thus more similar to that of the adult population than to that of 12-15-year-olds.

Deaths

There were no deaths among participants 12-15 years of age or 16-25 years of age during the reporting period of Dose 1 to the data cutoff date.

AEs leading to study withdrawal

12-15-year-olds: 2 BNT162b2 recipients and no placebo recipients withdrew from the study due to an AE; one BNT162b2 recipient experienced fever (peak T40.3 ºC) [non-serious AE] starting 2 days after BNT162b2 Dose 1 and resolved after 2 days, and the other BNT162b2 recipient was hospitalized for exacerbation of pre-existing anxiety and depression (both SAEs; described above). The study investigator and FDA considered only the AE of fever to be related to vaccination.

Comparator group of 16-25-year-olds (safety population): please see Supplemental Safety Data section.

Pregnancies

12-15-year-olds: no pregnancies reported up to data cut-off of March 13, 2021.

Comparator group of 16-25-year-olds (safety population): 9 pregnancies (3 BNT162b2, 6 placebo) were reported through the cut-off date of March 13, 2021:

- BNT162b2 group: 1 pregnancy was ongoing at the time of data cut-off. For the other 2 participants, pregnancy exposure occurred >30 days after Dose 1; 1 participant discontinued from the study and the other participant was lost to follow-up.
- Placebo group: 3 pregnancies were ongoing at the time of data cut-off, and spontaneous abortion occurred in 1 participant. For the remaining 2 participants, pregnancy exposure occurred 11 days and 23 days, respectively, after placebo dose 1; both participants discontinued from the study. Additional information will be requested during the BLA review period.

Supplemental Safety Data

Participants 16-55 years of age: The Phase 2/3 safety population with data cut-off of March 13, 2021, consisted of 26,164 participants 16-55 years of age (13,069 BNT162b2 recipients, 13,095 placebo recipients); 82.5% of BNT162b2 recipients and 84.4% of placebo recipients had 2 to <6 months of follow-up after Dose 2; 10.4% of BNT162b2 recipients and 8.2% of placebo recipients had ≥6 months of follow-up after Dose 2. Follow-up time contributing to the supplemental safety data was limited to follow-up prior to unblinding of study participants and crossover of placebo recipients.

AEs of clinical interest

Dose 1 to participant's unblinding date

Non-serious AEs

- *Lymphadenopathy*: Among 16-55-year-olds, 67 BNT162b2 recipients and 4 placebo recipients reported lymphadenopathy, of which 3 BNT162b2 recipients reported lymphadenopathy after the EUA data cut-off date of November 14, 2020. Lymphadenopathy occurred within 2-4 days after vaccination (usually after Dose 2), was located in the arm/neck regions (i.e., axilla, cervical, supraclavicular), and resolved within approximately 1 week of onset, all which FDA considers plausibly related to vaccination.
- *Bell's Palsy/Facial Paralysis/Facial Paresis*: No additional cases were reported since those described in the original EUA.[1]
- *DVT*: 1 BNT162b2 recipient and 1 placebo recipient reported DVT that were characterized as non-serious AEs. The BNT162b2 recipient developed a DVT in the leg 14 days after Dose 2, resolved after 6 days, and assessed by the study investigator as unrelated to vaccination; no hematologic results or medical intervention details were provided. The placebo recipient developed a DVT in the leg 85 days after placebo dose 2 that resolved after 1 day and was attributed by the study investigator to metabolic causes. No further information was provided.

SAEs

- *Anaphylaxis:* No additional cases were reported from November 20, 2020 to March 13, 2021 cut-off date.
- *Appendicitis:* 13 BNT162b2 and 7 placebo recipients reported appendicitis, of which 5 occurred in each of the BNT162b2 and placebo groups after the EUA data cut-off date of November 14, 2020; overall, among 16-25-year-olds, 1 BNT162b2 recipient and 0 placebo recipients reported appendicitis. All of the participants reporting appendicitis recovered. At this time, there is no clear basis upon which to suspect that the imbalance among vaccine and placebo 16-55-year-olds represents a vaccine-related risk.
- *DVT:* A total of 7 participants (4 BNT162b2 recipients, 3 placebo recipients) reported 9 SAEs:
  - 2 BNT162 recipients reported a DVT (unspecified location [n=1], leg [n=1]) 11 days after Dose 1 and 19 days after Dose 2, respectively. The first participant consequently developed a pulmonary embolism (PE). The DVT and PE resolved; the study investigator attributed the DVT to the participant's pre-existing type 1 diabetes mellitus. For the second participant, the event was ongoing at the time of the data cut-off date (March 13, 2021); the study investigator attributed the DVT to a recent ankle fracture in the same limb. No further information was provided for either participant.
  - The remaining 5 participants (2 BNT162b2 recipients, 3 placebo recipients) developed DVTs 71-115 days after study intervention Dose 2. The 2 BNT162b2 recipients both reported DVTs in the legs bilaterally with consequent PEs; all events resolved and the causes of the DVTs are unknown. Two placebo recipients both reported DVTs in the leg, which the study investigator attributed to sport-related trauma and reduced mobility during quarantine, respectively; the event is ongoing for the first placebo recipient and resolved for the second placebo recipient. The third placebo recipient reported DVT in the arm, the cause is unknown, and the event was ongoing at the time of the data cut-off date. No hematologic results or treatment intervention information was provided for any of the 7 participants.

The clinical features of these thromboembolic SAEs do not appear to be similar to cases of thrombosis with thrombocytopenia syndrome (TTS) reported following adenovirus-vectored COVID-19 vaccines, and post-authorization surveillance of adverse events following >130 million doses of Pfizer-BioNTech COVID-19 Vaccine in individuals 16 years of age and older has not raised a signal for TTS.

Other non-serious, unsolicited AEs

Dose 1 through 30 days after Dose 2

As with the safety data submitted in support of the original EUA request (data cut-off of November 14, 2020), the overall frequency of unsolicited, non-serious adverse events through the data cut-off of March 13, 2021, was higher in the BNT162b2 group (24.0%) compared to placebo group (4.7%).This imbalance was primarily attributed to local reactions and systemic adverse events in participants not in the reactogenicity subset and consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. No new imbalances were identified in frequencies of AEs from Dose 1 through 30 days after Dose 2 suggesting a causal relationship to BNT162b2, aside from previously identified imbalances in hypersensitivity reactions and Bell's palsy.

Dose 1 to participant's unblinding date

There were no newly identified notable patterns or numerical imbalances between treatment groups for specific categories (SOC and PT) of non-serious adverse events, including other neurologic, neuro-inflammatory events, that would suggest a causal relationship to BNT162b2 vaccine.

Other SAEs

Dose 1 through 30 days after Dose 2

Overall, the proportions of participants reporting at least 1 SAE in ongoing follow-up were the same in the BNT162b2 group (0.4%) as the placebo group (0.4%).

No additional SAEs in the BNT162b2 group considered related to vaccination by the study investigator were reported between the EUA data cutoff November 14, 2020 and March 13, 2021.

Dose 1 to participant's unblinding date

Eleven participants (3 BNT162b2 recipients, 8 placebo recipients) withdrew from the study due to at least 1 SAE: BNT162b2 group: lymphadenopathy (n=1), gastric adenocarcinoma (n=1), CNS metastases (n=1); placebo group: atrial fibrillation (n=1), visual impairment (n=1), diverticular perforation (n=1), drug overdose (n=1), amnesia (n=1), depression (n=1), suicide attempt (n=1), and respiratory arrest (n=1). Only the SAE of lymphadenopathy (reviewed under the original EUA request) was assessed by FDA as related to BNT162b2.[1]

There were 3 deaths in the BNT162b2 group and 4 deaths in the placebo group. The deaths in the vaccine group occurred at 86, 88, and 113 days after Dose 2, respectively, in participants who were 51-54 years of age; the listed causes of death (listed in the same order) were congestive heart failure, cardio-respiratory arrest and metastatic lung cancer. None of the reported deaths in BNT162b2 recipients were considered related to vaccination by the investigator or the FDA.

3.3 Data from Post-Authorization Safety Surveillance in Vaccine Participants 16 Years of Age and Older

As of April 20, 2021, 8,472 Pfizer-BioNTech COVID-19 Vaccine adverse event reports categorized as serious have been received and processed (coded, redacted, and quality assurance performed) by the Vaccine Adverse Event Reporting System (VAERS). The most common PTs among all VAERS reports are headache (n=9,126, 8.9%), chills (n=6,723, 6.6%), fatigue (n=6,720, 6.6%), pyrexia (6,565, 6.5%), pain (n=6,236, 6.1%), nausea (n=5,107, 5.0%), dizziness (n=4,671, 4.6%), pain in extremity (n=3,410, 3.3%), myalgia (n=3,225, 3.2%), and dyspnea (n=2,624, 2.6%). Other than anaphylaxis (discussed below), FDA review of VAERS reports, including serious and death reports, has not identified new safety concerns.

Data mining query with the Empirica Signal tool was performed on April 21, 2021 for each of the four Main Views (All Signals from Age Groups, All Signals from Gender, All Signals from Serious/Fatal, and All Signals from US/All VAERS). The data lock point was April 16, 2021. The alert score for disproportional reporting uses the lower bound of 95% confidence interval of

Empirical Bayesian geometric mean, EB05 >2.0. An EB05 of 2.064 was found for the PT 'Body Temperature' in adults ages 45-64.9 years of age. There were no other PTs with an EB05 >2.0.

Shortly after the issuance of the EUA, FDA received several reports of anaphylaxis following administration of the Pfizer-BioNTech COVID-19 Vaccine. Cases of anaphylaxis in the post-authorization experience are monitored by the Centers for Disease Control and Prevention (CDC) and FDA. Incoming VAERS reports are screened by CDC for potential cases of anaphylaxis. Additional clinical details are obtained by CDC staff by contacting the VAERS reporter and through review of medical records. Cases are classified as anaphylaxis using Brighton criteria. A case that meets the definition of Brighton Levels 1-3 is considered a case of anaphylaxis. Given the complexity of the Brighton criteria that require detailed clinical information, cases of anaphylaxis identified and classified by CDC are used. As of April 26, 2021, there have been 56 confirmed cases of anaphylaxis following the Pfizer-BioNTech COVID-19 Vaccine. Of the 56 cases, 51 (91.1%) are female and five (8.9%) are male. The median age is 39 years (range 27-67 years, unreported in one case). The time to onset from vaccination to the onset of symptoms of anaphylaxis ranged from immediately to 19 hours (unreported in three cases). Twenty-three (41.1%) cases met the criteria for Brighton Level 1, 30 (53.6%) were Brighton Level 2, and three (5.4%) were Brighton Level 3. As of April 26, 2021, a total of 120,774,248 doses of Pfizer-BioNTech COVID-19 Vaccine have been administered for an anaphylaxis reporting rate of 0.46 per million doses.

4. FDA Review of Other Information Submitted in Support of the EUA

4.1 Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants 12-15 years of age who originally received placebo and who are eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all participants ≥12 years of age who received placebo will be offered BNT162b2 after completing 6 months of follow-up after Dose 2 (if they have not already received it by this time). The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow-up period of 18 months, with a visit 1-month post-vaccination and subsequent phone contacts at 1, 6, and 18 months post-vaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

4.2 Pharmacovigilance Activities

Pfizer submitted a revised Pharmacovigilance Plan to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor includes anaphylaxis as an important identified risk. Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease is included as an important potential risk. Use in pregnancy and lactation, vaccine effectiveness, and use in pediatric individuals <12 years of age are areas the Sponsor identified as missing information. Division of Epidemiology recommendations are as follows:

1. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
    - SAEs (irrespective of attribution to vaccination)
    - Cases of multisystem inflammatory syndrome in children

- Cases of COVID-19 that result in hospitalization or death

2. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and AESIs
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
   - Newly identified safety concerns in the interval
   - Actions taken since the last report because of adverse experiences (e.g., changes made to Fact Sheet for Vaccination Providers, changes made to studies or studies initiated)

3. The Sponsor will conduct one or more post-authorization observational studies to evaluate the association between BNT162b2 and a pre-specified list of AESIs, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized BNT162b2 under this EUA amendment to include individuals 12-15 years of age in the general U.S. population, populations of interest such as pregnant women, immunocompromised individuals, and subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. The Sponsor will provide protocols and status update reports with agreed-upon study designs and milestone dates. The Sponsor has proposed the following planned active surveillance study that will include adolescents ages 12-15 years:
   - Study Protocol Number C4591009. This is a post-approval observational study using real-world data to assess the association between the BNT162b2 and safety events of interest among persons administered the vaccine in the U.S. population and in populations of interest such as pregnant women, immunocompromised persons, and in persons with a prior history of COVID-19 infection. This study will use electronic health records and claims data from data partners participating in the Sentinel System (anticipated protocol submission: August 31, 2021).

     Of note, the Sponsor submitted a clinical study protocol to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor pregnancy following administration of the vaccine within populations expected to receive the vaccine under EUA.

4. The Sponsor submitted a protocol for a vaccine effectiveness study:
   - Study Protocol Number C4591014. This study estimates vaccine effectiveness of two doses of the BNT162b2 in preventing hospitalization due to SARS-CoV-2 infection in individuals ≥16 years of age. Other objectives include evaluation of vaccine effectiveness after one dose, emergency department admission, specific variants, and other populations of interest. This study will utilize the Kaiser Permanente Southern California database. According to a response to an Information Request, the Sponsor plans to amend this protocol to include patients ages 12-15 years.

5. Active surveillance of vaccine recipients via the v-safe program: V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The

system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the participant received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate. V-safe may be modified to allow adolescents to self-register and report to v-safe, and a pathway created for a parent/guardian to report on behalf of younger children.

4.3 Chemistry, Manufacturing, and Control (CMC) Information

The Sponsor did not submit any new CMC information with this EUA amendment. Therefore, as determined during review of the original EUA request, the Pfizer-BioNTech COVID-19 Vaccine is manufactured with sufficient quality and consistency to support the proposed use under EUA.[1]

4.4 Clinical Assay Information

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. The Cepheid Xpert Xpress RT-PCR assay is used to assess viral infection of the subjects before vaccination and to confirm COVID-19 cases during study follow-up. The Roche Elecsys Anti-SARS-CoV-2 assay is used to assess serostatus of the subjects before vaccination. Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended use in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

4.5 Inspections of Clinical Study Sites

Bioresearch Monitoring inspections were conducted at three domestic clinical investigator sites participating in the conduct of study C4591001 that included pediatric subjects 12 through 15 years of age. Based on the review of the inspection reports, the inspections did not reveal problems impacting the data submitted in support of this EUA amendment.

4.6 EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, and Fact Sheet for Participants were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

5. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

5.1 Known Benefits

The known benefit among participants of the Pfizer-BioNTech COVID-19 vaccine 12-15 years of age is reduction in the risk of confirmed COVID-19, relative to placebo, occurring at least 7 days after Dose 2, and reduction in the risk of confirmed COVID-19, relative to placebo, occurring between Dose 1 and 7 days after Dose 2 (with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1).

Vaccine effectiveness in participants 12-15 years of age was inferred by immunobridging, based on a comparison of immune responses in participants 12-15 years of age with those of young adults 16-25 years of age (in whom VE has been demonstrated). The protocol-specified 2-dose vaccination regimen was also highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen in participants 12-15 years of age, which (although based on a small number of cases in descriptive analyses) provides compelling direct evidence of clinical benefit in addition to the immunobridging data.

5.2 Unknown Benefits/Data Gaps

The unknown benefits and data gaps associated with the Pfizer-BioNTech COVID-19 vaccine when used in adolescents 12-15 years of age are the same as those detailed in the memorandum authorizing the vaccine for emergency use in for the individuals 16 years of age and older.[1] They relate to:

- Duration of protection
- Effectiveness in certain populations at high risk of severe COVID-19
- Effectiveness in individuals previously infected with SARS-CoV-2
- Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections
- Vaccine effectiveness against asymptomatic infection
- Vaccine effectiveness against long-term effects of COVID-19 disease
- Vaccine effectiveness against mortality
- Vaccine effectiveness against transmission of SARS-CoV-2

This EUA Amendment provides additional insight for the following unknown benefit/data gap that was previously considered**:**

Effectiveness in pediatric populations

The study enrollment is limited to participants 12 years of age and older. No data are available at this time to evaluate the vaccine effectiveness in children under 12 years of age.

5.3 Known Risks

In individuals 12-15 years of age, there were higher frequencies of solicited local adverse reactions/systemic adverse events and lymphadenopathy in vaccine recipients than placebo recipients. Overall (after any dose), common solicited adverse reactions and events after BNT162b2 vaccination included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in

0.0%-2.4% of 12-15-year-old BNT162b2 recipients; such events were more frequent after BNT162b2 Dose 2 than after BNT162b2 Dose 1 and more frequent in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds.

Among unsolicited adverse events reported from Dose 1 to 1 month after Dose 2, lymphadenopathy considered as related to study intervention by the study investigator and FDA occurred more frequently in the vaccine group (n=7) than the placebo group (n=1). The number of subjects reporting hypersensitivity-related adverse events was numerically lower in the vaccine group compared with the placebo group (6 [0.53%] vs. 10 [0.89%]).

Serious adverse events, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2.

Although only 2 recipients (1 BNT162b2, 1 placebo) reported symptoms consistent with pre-syncope on the day of vaccination, vasovagal reactions are not uncommon in adolescents following vaccinations and other medical procedures involving needlesticks. The vaccine Fact Sheets and Prescribing Information for healthcare providers include a warning about measures to avoid injury following vasovagal/syncopal episodes in the immediate post-vaccination period.

Anaphylaxis, primarily among individuals with a history of severe allergic reactions to other medications or foods, has been documented to occur at a rate of 0.46 cases per million doses among vaccine recipients 16 years of age and older (similar to reported rates of anaphylaxis following licensed preventive vaccines). Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the pharmacovigilance plan for the vaccine.

5.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 12 years of age, pregnant and lactating individuals, and immunocompromised individuals. Safety data in adolescents previously infected with SARS-CoV-2 are limited; however, re-infection has been documented and could be prevented by vaccination, and available data do not suggest safety concerns that would result in unfavorable benefit/risk in previously infected individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals 12-15 years of age may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of 3,769 participants described from Dose 1 through the data cutoff date (March 13, 2021). Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

6. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in Section 2 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 3 of this review, the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2 in adolescents 12-15 years of age. Vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analyses, the GMR of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups. In the supplemental efficacy analyses, VE after 7 days post Dose 2 was 100%, (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0 (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

- Based on the data summarized in Sections 3 and 4 of this review and assessment of benefits and risks in Section 5 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age. Known benefits include reduction in the risk of confirmed COVID-19. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, fatigue,

headache, chills, muscle pain, fever and joint pain), less commonly lymphadenopathy, and rarely anaphylaxis based on experience in Pfizer-BioNTech COVID-19 vaccine recipients 16 years of age and older with history of severe allergic reactions to other medications or foods. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up, risks associated with vaccination of specific populations such as children younger than 12 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, or available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

7. Appendix A. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

Source: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

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Exhibit 6

Moderna: Fact Sheet for Recipients and Caregivers (Mar. 26, 2021 (revised))

FACT SHEET FOR RECIPIENTS AND CAREGIVERS
EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) IN INDIVIDUALS 18 YEARS OF AGE AND OLDER

You are being offered the Moderna COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of the Moderna COVID-19 Vaccine, which you may receive because there is currently a pandemic of COVID-19.

The Moderna COVID-19 Vaccine is a vaccine and may prevent you from getting COVID-19. There is no U.S. Food and Drug Administration (FDA) approved vaccine to prevent COVID-19.

Read this Fact Sheet for information about the Moderna COVID-19 Vaccine. Talk to the vaccination provider if you have questions. It is your choice to receive the Moderna COVID-19 Vaccine.

The Moderna COVID-19 Vaccine is administered as a 2-dose series, 1 month apart, into the muscle.

The Moderna COVID-19 Vaccine may not protect everyone.

This Fact Sheet may have been updated. For the most recent Fact Sheet, please visit www.modernatx.com/covid19vaccine-eua.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?
COVID-19 is caused by a coronavirus called SARS-CoV-2. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, 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.

WHAT IS THE MODERNA COVID-19 VACCINE?
The Moderna COVID-19 Vaccine is an unapproved vaccine that may prevent COVID-19. There is no FDA-approved vaccine to prevent COVID-19.

The FDA has authorized the emergency use of the Moderna COVID-19 Vaccine to prevent COVID-19 in individuals 18 years of age and older under an Emergency Use Authorization (EUA).

For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE MODERNA COVID-19 VACCINE?

Tell your vaccination provider about all of your medical conditions, including if you:

- have any allergies
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects your immune system
- are pregnant or plan to become pregnant
- are breastfeeding
- have received another COVID-19 vaccine

WHO SHOULD GET THE MODERNA COVID-19 VACCINE?

FDA has authorized the emergency use of the Moderna COVID-19 Vaccine in individuals 18 years of age and older.

WHO SHOULD NOT GET THE MODERNA COVID-19 VACCINE?

You should not get the Moderna COVID-19 Vaccine if you:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine

WHAT ARE THE INGREDIENTS IN THE MODERNA COVID-19 VACCINE?

The Moderna COVID-19 Vaccine contains the following ingredients: messenger ribonucleic acid (mRNA), lipids (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate trihydrate, and sucrose.

HOW IS THE MODERNA COVID-19 VACCINE GIVEN?

The Moderna COVID-19 Vaccine will be given to you as an injection into the muscle.

The Moderna COVID-19 Vaccine vaccination series is 2 doses given 1 month apart.

If you receive one dose of the Moderna COVID-19 Vaccine, you should receive a second dose of the same vaccine 1 month later to complete the vaccination series.

HAS THE MODERNA COVID-19 VACCINE BEEN USED BEFORE?

The Moderna COVID-19 Vaccine is an unapproved vaccine. In clinical trials, approximately 15,400 individuals 18 years of age and older have received at least 1 dose of the Moderna COVID-19 Vaccine.

WHAT ARE THE BENEFITS OF THE MODERNA COVID-19 VACCINE?

In an ongoing clinical trial, the Moderna COVID-19 Vaccine has been shown to prevent COVID-19 following 2 doses given 1 month apart. The duration of protection against COVID-19 is currently unknown.

WHAT ARE THE RISKS OF THE MODERNA COVID-19 VACCINE?
There is a remote chance that the Moderna COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Moderna COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Dizziness and weakness

Side effects that have been reported in a clinical trial with the Moderna COVID-19 Vaccine include:

- Injection site reactions: pain, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling (hardness), and redness
- General side effects: fatigue, headache, muscle pain, joint pain, chills, nausea and vomiting, and fever

Side effects that have been reported during post-authorization use of the Moderna COVID-19 Vaccine include:

- Severe allergic reactions

These may not be all the possible side effects of the Moderna COVID-19 Vaccine. Serious and unexpected side effects may occur. The Moderna COVID-19 Vaccine is still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?
If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Call the vaccination provider or your healthcare provider if you have any side effects that bother you or do not go away.

Report vaccine side effects to **FDA/CDC Vaccine Adverse Event Reporting System (VAERS)**. The VAERS toll-free number is 1-800-822-7967 or report online to https://vaers.hhs.gov/reportevent.html. Please include "Moderna COVID-19 Vaccine EUA" in the first line of box #18 of the report form.

In addition, you can report side effects to ModernaTX, Inc. at 1-866-MODERNA (1-866-663-3762).

You may also be given an option to enroll in **v-safe. V-safe** is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. **V-safe** asks questions that help CDC monitor the safety of COVID-19 vaccines. **V-safe** also provides second-dose reminders if

needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information on how to sign up, visit: www.cdc.gov/vsafe.

WHAT IF I DECIDE NOT TO GET THE MODERNA COVID-19 VACCINE?
It is your choice to receive or not receive the Moderna COVID-19 Vaccine. Should you decide not to receive it, it will not change your standard medical care.

ARE OTHER CHOICES AVAILABLE FOR PREVENTING COVID-19 BESIDES MODERNA COVID-19 VACCINE?
Currently, there is no FDA-approved alternative vaccine available for prevention of COVID-19. Other vaccines to prevent COVID-19 may be available under Emergency Use Authorization.

CAN I RECEIVE THE MODERNA COVID-19 VACCINE WITH OTHER VACCINES?
There is no information on the use of the Moderna COVID-19 Vaccine with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?
If you are pregnant or breastfeeding, discuss your options with your healthcare provider.

WILL THE MODERNA COVID-19 VACCINE GIVE ME COVID-19?
No. The Moderna COVID-19 Vaccine does not contain SARS-CoV-2 and cannot give you COVID-19.

KEEP YOUR VACCINATION CARD
When you receive your first dose, you will get a vaccination card to show you when to return for your second dose of the Moderna COVID-19 Vaccine. Remember to bring your card when you return.

ADDITIONAL INFORMATION
If you have questions, visit the website or call the telephone number provided below.

To access the most recent Fact Sheets, please scan the QR code provided below.

Moderna COVID-19 Vaccine website	Telephone number
www.modernatx.com/covid19vaccine-eua	1-866-MODERNA (1-866-663-3762)

HOW CAN I LEARN MORE?

- Ask the vaccination provider
- Visit CDC at https://www.cdc.gov/coronavirus/2019-ncov/index.html
- Visit FDA at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
- Contact your state or local public health department

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?

The vaccination provider may include your vaccination information in your state/local jurisdiction's Immunization Information System (IIS) or other designated system. This will ensure that you receive the same vaccine when you return for the second dose. For more information about IISs, visit: https://www.cdc.gov/vaccines/programs/iis/about.html.

CAN I BE CHARGED AN ADMINISTRATION FEE FOR RECEIPT OF THE COVID-19 VACCINE?

No. At this time, the provider cannot charge you for a vaccine dose and you cannot be charged an out-of-pocket vaccine administration fee or any other fee if only receiving a COVID-19 vaccination. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients).

WHERE CAN I REPORT CASES OF SUSPECTED FRAUD?

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

WHAT IS THE COUNTERMEASURES INJURY COMPENSATION PROGRAM?

The Countermeasures Injury Compensation Program (CICP) is a federal program that may help pay for costs of medical care and other specific expenses of certain people who have been seriously injured by certain medicines or vaccines, including this vaccine. Generally, a claim must be submitted to the CICP within one (1) year from the date of receiving the vaccine. To learn more about this program, visit www.hrsa.gov/cicp/ or call 1-855-266-2427.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?

The United States FDA has made the Moderna COVID-19 Vaccine available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

The Moderna COVID-19 Vaccine has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of the scientific evidence available showing that the product may be effective to prevent COVID-19 during the COVID-19 pandemic and that the known and potential benefits of the product outweigh the known and potential risks of the product. All of

these criteria must be met to allow for the product to be used during the COVID-19 pandemic.

The EUA for the Moderna COVID-19 Vaccine is in effect for the duration of the COVID-19 EUA declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

Moderna US, Inc.
Cambridge, MA 02139

Patent(s): www.modernatx.com/patents
Revised: Mar/26/2021

Scan to capture that this Fact Sheet was provided to vaccine recipient for the electronic medical records/immunization information systems.

Barcode Date: 04/2021

Exhibit 7

Moderna: Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) (Mar. 31, 2021 (revised))

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)
EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **MODERNA COVID-19 VACCINE**, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

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 Multisystem Inflammatory Syndrome (MIS) in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Moderna COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR MODERNA COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Moderna COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.5 mL each) 1 month apart.

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.modernatx.com/covid19vaccine-eua.

For information on clinical trials that are testing the use of the Moderna COVID-19 Vaccine for active immunization against 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 and body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling
The information in this Fact Sheet supersedes the information on the vial and carton labels.

During storage, minimize exposure to room light.

The Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50º to -15ºC (-58º to 5ºF). Store in the original carton to protect from light.

Do not store on dry ice or below -50ºC (-58ºF). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F).

Vials may be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use.

Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

Transportation of Thawed Vials at 2° to 8°C (35° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (35° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (35° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (35° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (35° to 46°F) until use.

Dosing and Schedule
The Moderna COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart.

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

Dose Preparation

- The Moderna COVID-19 Vaccine multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

Vial	Thaw in Refrigerator	Thaw at Room Temperature
Maximum 11-Dose Vial (range: 10-11 doses)	Thaw in refrigerated conditions between 2° to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour.
Maximum 15-Dose Vial (range: 13-15 doses)	Thaw in refrigerated conditions between 2° to 8°C for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- The Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the Moderna COVID-19 Vaccine vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
- The Moderna COVID-19 Vaccine is supplied in two multiple-dose vial presentations:
    - A multiple-dose vial containing a maximum of 11 doses: range 10-11 doses (0.5 mL each).
    - A multiple-dose vial containing a maximum of 15 doses: range 13-15 doses (0.5 mL each).
- Depending on the syringes and needles used for each dose, there may not be sufficient volume to extract more than 10 doses from the maximum of 11 doses vial or more than 13 doses from the maximum of 15 doses vial. Irrespective of the type of syringe and needle:
    - Each dose must contain 0.5 mL of vaccine.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
    - Pierce the stopper at a different site each time.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 12 hours. Do not refreeze.

Administration

Visually inspect each dose of the Moderna COVID-19 Vaccine in the dosing syringe prior to administration. The white to off-white suspension may contain white or translucent product-related particulates. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no other particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains other particulate matter.

Administer the Moderna COVID-19 Vaccine intramuscularly.

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

WARNINGS
Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine.

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

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

The Moderna COVID-19 Vaccine may not protect all vaccine recipients.

ADVERSE REACTIONS
Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site. *(See Full EUA Prescribing Information)*

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Moderna COVID-19 Vaccine.

USE WITH OTHER VACCINES
There is no information on the co-administration of the Moderna COVID-19 Vaccine 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 "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.modernatx.com/covid19vaccine-eua to obtain the Fact Sheet) prior to the individual receiving each dose of the Moderna COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Moderna COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse the Moderna COVID-19

Vaccine.
- The significant known and potential risks and benefits of the Moderna COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives

For information on clinical trials that are evaluating the use of the Moderna COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Moderna COVID-19 Vaccine.

Provide the **v-safe** information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in **v-safe**. **V-safe** is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. **V-safe** asks questions that help CDC monitor the safety of COVID-19 vaccines. **V-safe** also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR MODERNA COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

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

1. The Moderna COVID-19 Vaccine is authorized for use in individuals 18 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Moderna COVID-19 Vaccine or their caregiver information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving the Moderna COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
    - vaccine administration errors whether or not associated with an adverse event,
    - serious adverse events* (irrespective of attribution to vaccination),
    - cases of Multisystem Inflammatory Syndrome (MIS) in adults, and
    - cases of COVID-19 that result in hospitalization or death.

    Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html.

For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words "Moderna COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Moderna COVID-19 Vaccine to recipients.

*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 one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND MODERNATX, INC.
Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to ModernaTX, Inc. using the contact information below or by providing a copy of the VAERS form to ModernaTX, Inc.

Email	Fax number	Telephone number
ModernaPV@modernatx.com	1-866-599-1342	1-866-MODERNA (1-866-663-3762)

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

To access the most recent Moderna COVID-19 Vaccine Fact Sheets, please scan the QR code or visit the website provided below.

Website	Telephone number
www.modernatx.com/covid19vaccine-eua 	1-866-MODERNA (1-866-663-3762)

AVAILABLE ALTERNATIVES
There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM
This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

AUTHORITY FOR ISSUANCE OF THE EUA
The Secretary of the Department 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, the FDA has issued an EUA for the unapproved product, Moderna COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

FDA issued this EUA, based on ModernaTX, Inc.'s request and submitted data.

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

This EUA for the Moderna COVID-19 Vaccine 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.

COUNTERMEASURES INJURY COMPENSATION PROGRAM

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the vaccines to prevent COVID-19, visit http://www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Moderna US, Inc.
Cambridge, MA 02139

Patent(s): www.modernatx.com/patents
Revised: Mar/31/2021

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

MODERNA COVID-19 VACCINE

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

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

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FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Moderna COVID-19 Vaccine 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 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

- The Moderna COVID-19 Vaccine multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- Remove the required number of vial(s) from storage and thaw each vial before use following the instructions below.

Vial	Thaw in Refrigerator	Thaw at Room Temperature
Maximum 11-Dose Vial (range: 10-11 doses)	Thaw in refrigerated conditions between 2° to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour.
Maximum 15-Dose Vial (range: 13-15 doses)	Thaw in refrigerated conditions between 2° to 8°C for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw at room temperature between 15° to 25°C for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- The Moderna COVID-19 Vaccine is a white to off-white suspension. It may contain white or translucent product-related particulates. Visually inspect the Moderna COVID-19 Vaccine vials for other particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
- The Moderna COVID-19 Vaccine is supplied in two multiple-dose vial presentations:
    - A multiple-dose vial containing a maximum of 11 doses: range 10-11 doses (0.5 mL each).
    - A multiple-dose vial containing a maximum of 15 doses: range 13-15 doses (0.5 mL each).
- Depending on the syringes and needles used for each dose, there may not be sufficient volume to extract more than 10 doses from the maximum of 11 doses vial or more than 13 doses from the maximum of 15 doses vial. Irrespective of the type of syringe and needle:
    - Each dose must contain 0.5 mL of vaccine.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
    - Pierce the stopper at a different site each time.
- After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Record the date and time of first use on the Moderna COVID-19 Vaccine vial label. Discard vial after 12 hours. Do not refreeze.

2.2 Administration

Visually inspect each dose of the Moderna COVID-19 Vaccine in the dosing syringe prior to administration. The white to off-white suspension may contain white or translucent product-related particulates. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no other particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains other particulate matter.

Administer the Moderna COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule
The Moderna COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart.

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

3 DOSAGE FORMS AND STRENGTHS

Moderna COVID-19 Vaccine is a suspension for intramuscular injection. A single dose is 0.5 mL.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine.

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

5.2 Altered Immunocompetence
Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished response to the Moderna COVID-19 Vaccine.

5.3 Limitations of Vaccine Effectiveness
The Moderna COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multi-inflammatory Syndrome (MIS) in adults, and hospitalized or fatal cases of

COVID-19 following vaccination with the Moderna COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to ModernaTX, Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and ModernaTX, Inc.

In clinical studies, the adverse reactions in participants 18 years of age and older were pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23.0%), axillary swelling/tenderness (19.8%), fever (15.5%), swelling at the injection site (14.7%), and erythema at the injection site (10.0%).

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

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

Overall, 15,419 participants aged 18 years and older received at least one dose of Moderna COVID-19 Vaccine in three clinical trials (NCT04283461, NCT04405076, and NCT04470427).

The safety of Moderna COVID-19 Vaccine was evaluated in an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of Moderna COVID-19 Vaccine (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older. Overall, 52.7% were male, 47.3% were female, 20.5% were Hispanic or Latino, 79.2% were White, 10.2% were African American, 4.6% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Pacific Islander, 2.1% were other races, and 2.1% were Multiracial. Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.

Solicited Adverse Reactions

Data on solicited local and systemic adverse reactions and use of antipyretic medication were collected in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among participants receiving Moderna COVID-19 Vaccine (n=15,179) and participants receiving placebo (n=15,163) with at least 1 documented dose. Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants.

The reported number and percentage of the solicited local and systemic adverse reactions by age group and dose are presented in Table 1 and Table 2, respectively.

Table 1: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Within 7 Days* After Each Dose in Participants 18-64 Years (Solicited Safety Set, Dose 1 and Dose 2)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=10,985) n (%)	**Dose 1** (N=11,407) n (%)	**Dose 2** (N=10,918) n (%)
Local Adverse Reactions				
Pain	9,908 (86.9)	9,873 (89.9)	2,177 (19.1)	2,040 (18.7)
Pain, Grade 3[b]	366 (3.2)	506 (4.6)	23 (0.2)	22 (0.2)
Axillary swelling/tenderness	1,322 (11.6)	1,775 (16.2)	567 (5.0)	470 (4.3)
Axillary swelling/tenderness, Grade 3[b]	37 (0.3)	46 (0.4)	13 (0.1)	11 (0.1)
Swelling (hardness) ≥25 mm	767 (6.7)	1,389 (12.6)	34 (0.3)	36 (0.3)
Swelling (hardness), Grade 3[c]	62 (0.5)	182 (1.7)	3 (<0.1)	4 (<0.1)
Erythema (redness) ≥25 mm	344 (3.0)	982 (8.9)	47 (0.4)	43 (0.4)
Erythema (redness), Grade 3[c]	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)
Systemic Adverse Reactions				
Fatigue	4,384 (38.4)	7,430 (67.6)	3,282 (28.8)	2,687 (24.6)
Fatigue, Grade 3[d]	120 (1.1)	1,174 (10.7)	83 (0.7)	86 (0.8)
Fatigue, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache	4,030 (35.3)	6,898 (62.8)	3,304 (29.0)	2,760 (25.3)
Headache, Grade 3[f]	219 (1.9)	553 (5.0)	162 (1.4)	129 (1.2)
Myalgia	2,699 (23.7)	6,769 (61.6)	1,628 (14.3)	1,411 (12.9)
Myalgia, Grade 3[d]	73 (0.6)	1,113 (10.1)	38 (0.3)	42 (0.4)
Arthralgia	1,893 (16.6)	4,993 (45.5)	1,327 (11.6)	1,172 (10.7)
Arthralgia, Grade 3[d]	47 (0.4)	647 (5.9)	29 (0.3)	37 (0.3)
Arthralgia, Grade 4[e]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills	1,051 (9.2)	5,341 (48.6)	730 (6.4)	658 (6.0)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=11,406) n (%)	**Dose 2** (N=10,985) n (%)	**Dose 1** (N=11,407) n (%)	**Dose 2** (N=10,918) n (%)
Chills, Grade 3[g]	17 (0.1)	164 (1.5)	8 (<0.1)	15 (0.1)
Nausea/vomiting	1,068 (9.4)	2,348 (21.4)	908 (8.0)	801 (7.3)
Nausea/vomiting, Grade 3[h]	6 (<0.1)	10 (<0.1)	8 (<0.1)	8 (<0.1)
Fever	105 (0.9)	1,908 (17.4)	37 (0.3)	39 (0.4)
Fever, Grade 3[i]	10 (<0.1)	184 (1.7)	1 (<0.1)	2 (<0.1)
Fever, Grade 4[j]	4 (<0.1)	12 (0.1)	4 (<0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	6,292 (57.3)	1,523 (13.4)	1,248 (11.4)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).
[a] Placebo was a saline solution.
[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[e] Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.
[f] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[g] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[h] Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Table 2: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Within 7 Days* After Each Dose in Participants 65 Years and Older (Solicited Safety Set, Dose 1 and Dose 2)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=3,762) n (%)	**Dose 2** (N=3,692) n (%)	**Dose 1** (N=3,748) n (%)	**Dose 2** (N=3,648) n (%)
Local Adverse Reactions				
Pain	2,782 (74.0)	3,070 (83.2)	481 (12.8)	437 (12.0)
Pain, Grade 3[b]	50 (1.3)	98 (2.7)	32 (0.9)	18 (0.5)
Axillary swelling/tenderness	231 (6.1)	315 (8.5)	155 (4.1)	97 (2.7)
Axillary swelling/tenderness, Grade 3[b]	12 (0.3)	21 (0.6)	14 (0.4)	8 (0.2)

	Moderna COVID-19 Vaccine		Placebo[a]	
	Dose 1 (N=3,762) n (%)	**Dose 2** (N=3,692) n (%)	**Dose 1** (N=3,748) n (%)	**Dose 2** (N=3,648) n (%)
Swelling (hardness) ≥25 mm	165 (4.4)	400 (10.8)	18 (0.5)	13 (0.4)
Swelling (hardness), Grade 3[c]	20 (0.5)	72 (2.0)	3 (<0.1)	7 (0.2)
Erythema (redness) ≥25 mm	86 (2.3)	275 (7.5)	20 (0.5)	13 (0.4)
Erythema (redness), Grade 3[c]	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
Systemic Adverse Reactions				
Fatigue	1,251 (33.3)	2,152 (58.3)	851 (22.7)	716 (19.6)
Fatigue, Grade 3[d]	30 (0.8)	254 (6.9)	22 (0.6)	20 (0.5)
Headache	921 (24.5)	1,704 (46.2)	723 (19.3)	650 (17.8)
Headache, Grade 3[e]	52 (1.4)	106 (2.9)	34 (0.9)	33 (0.9)
Myalgia	742 (19.7)	1,739 (47.1)	443 (11.8)	398 (10.9)
Myalgia, Grade 3[d]	17 (0.5)	205 (5.6)	9 (0.2)	10 (0.3)
Arthralgia	618 (16.4)	1,291 (35.0)	456 (12.2)	397 (10.9)
Arthralgia, Grade 3[d]	13 (0.3)	123 (3.3)	8 (0.2)	7 (0.2)
Chills	202 (5.4)	1,141 (30.9)	148 (4.0)	151 (4.1)
Chills, Grade 3[f]	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194 (5.2)	437 (11.8)	166 (4.4)	133 (3.6)
Nausea/vomiting, Grade 3[g]	4 (0.1)	10 (0.3)	4 (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4[h]	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever	10 (0.3)	370 (10.0)	7 (0.2)	4 (0.1)
Fever, Grade 3[i]	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4[j]	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	1,546 (41.9)	477 (12.7)	329 (9.0)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).

[a] Placebo was a saline solution.

[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.
[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[e] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[f] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[g] Grade 3 Nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
[h] Grade 4 Nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.
[i] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.
[j] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Solicited local and systemic adverse reactions reported following administration of Moderna COVID-19 Vaccine had a median duration of 1 to 3 days.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

Unsolicited Adverse Events

Participants were monitored for unsolicited adverse events for up to 28 days following each dose and follow-up is ongoing. Serious adverse events and medically attended adverse events will be recorded for the entire study duration of 2 years. As of November 25, 2020, among participants who had received at least 1 dose of vaccine or placebo (vaccine=15,185, placebo=15,166), unsolicited adverse events that occurred within 28 days following each vaccination were reported by 23.9% of participants (n=3,632) who received Moderna COVID-19 Vaccine and 21.6% of participants (n=3,277) who received placebo. In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2.

Lymphadenopathy-related events that were not necessarily captured in the 7-day e-diary were reported by 1.1% of vaccine recipients and 0.6% of placebo recipients. These events included lymphadenopathy, lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass, which were plausibly related to vaccination. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness in the injected arm.

Hypersensitivity adverse events were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. Delayed injection site reactions that began >7 days after vaccination were reported in 1.2% of vaccine recipients and 0.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

Throughout the same period, there were three reports of Bell's palsy in the Moderna COVID-19 Vaccine group (one of which was a serious adverse event), which occurred 22, 28, and 32 days after vaccination, and one in the placebo group which occurred 17 days after vaccination. Currently available information on Bell's palsy 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 adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Moderna COVID-19 Vaccine.

Serious Adverse Events

As of November 25, 2020, serious adverse events were reported by 1.0% (n=147) of participants who received Moderna COVID-19 Vaccine and 1.0% (n=153) of participants who received placebo, one of which was the case of Bell's palsy which occurred 32 days following receipt of vaccine.

In these analyses, 87.9% of study participants had at least 28 days of follow-up after Dose 2, and the median follow-up time for all participants was 9 weeks after Dose 2.

There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination.

There was one serious adverse event of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination.

There were no other notable patterns or 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 Moderna COVID-19 Vaccine.

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 the MANDATORY reporting of the listed events following Moderna COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS)

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of multisystem inflammatory syndrome (MIS) in adults
- Cases of COVID-19 that results 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 one of the outcomes listed above.

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:
- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report, you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, 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 Moderna COVID-19 Vaccine
- 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 Moderna COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write “Moderna COVID-19 Vaccine 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).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to ModernaTX, Inc. using the contact information below or by providing a copy of the VAERS form to ModernaTX, Inc.

Email	Fax number	Telephone number
ModernaPV@modernatx.com	1-866-599-1342	1-866-MODERNA (1-866-663-3762)

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Moderna COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Moderna COVID-19 Vaccine during pregnancy. Women who are vaccinated with Moderna COVID-19 Vaccine during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. 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 Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of Moderna COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. 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 Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Safety and effectiveness have not been assessed in persons less than 18 years of age. Emergency Use Authorization of Moderna COVID-19 Vaccine does not include use in individuals younger than 18 years of age.

11.4 Geriatric Use

Clinical studies of Moderna COVID-19 Vaccine included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In an ongoing Phase 3 clinical study, 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 86.4% (95% CI 61.4, 95.2) compared to 95.6% (95% CI 90.6, 97.9) in participants 18 to <65 years of age *[see Clinical Trial Results and Supporting Data for EUA (18)]*. Overall, there were no notable differences in the safety profiles observed in participants 65 years of age and older and younger participants *[*see *Overall Safety Summary (6.1)]*.

13 DESCRIPTION

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection. Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each dose of the Moderna COVID-19 Vaccine contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose.

Moderna COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

A Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older is ongoing in the United States (NCT04470427). Randomization was stratified by age and health risk: 18 to <65 years of age without comorbidities (not at risk for progression to severe COVID-19), 18 to <65 years of age with comorbidities (at risk for progression to severe COVID-19), and 65 years of age and older with or without comorbidities. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable human immunodeficiency virus (HIV) infection. A total of 30,420 participants were randomized equally to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 24 months after the second dose.

The primary efficacy analysis population (referred to as the Per-Protocol Set) included 28,207 participants who received two doses (at 0 and 1 month) of either Moderna COVID-19 Vaccine (n=14,134) or placebo (n=14,073), and had a negative baseline SARS-CoV-2 status. In the Per-Protocol Set, 47.4% were female, 19.7% were Hispanic or Latino; 79.5% were White, 9.7% were African American, 4.6% were Asian, and 2.1% other races. The median age of participants was 53 years (range 18-95) and 25.3% of participants were 65 years of age and older. Of the study participants in the Per-Protocol Set, 18.5% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection) regardless of age. Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

Efficacy Against COVID-19

COVID-19 was defined based on the following criteria: The participant must have experienced at least two of the following systemic symptoms: fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one

NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

The median length of follow up for efficacy for participants in the study was 9 weeks post Dose 2. There were 11 COVID-19 cases in the Moderna COVID-19 Vaccine group and 185 cases in the placebo group, with a vaccine efficacy of 94.1% (95% confidence interval of 89.3% to 96.8%).

Table 3: Primary Efficacy Analysis: COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)†
Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

The subgroup analyses of vaccine efficacy are presented in Table 4.

Table 4: Subgroup Analyses of Vaccine Efficacy: COVID-19* Cases Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per- Protocol Set

Age Subgroup (Years)	Moderna COVID-19 Vaccine			Placebo			% Vaccine Efficacy (95% CI)*
	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom. Cases starting 14 days after Dose 2.
† VE and 95% CI from the stratified Cox proportional hazard model.

Severe COVID-19 was defined based on confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥30 per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room

air at sea level or PaO2/FIO2 <300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure <90 mmHg, diastolic BP <60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death.

Among all participants in the Per-Protocol Set analysis, which included COVID-19 cases confirmed by an adjudication committee, no cases of severe COVID-19 were reported in the Moderna COVID-19 Vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 person-years). One PCR-positive case of severe COVID-19 in a vaccine recipient was awaiting adjudication at the time of the analysis.

19 HOW SUPPLIED/STORAGE AND HANDLING

Moderna COVID-19 Vaccine Suspension for Intramuscular Injection Multiple-Dose Vials are supplied as follows:

NDC 80777-273-99	Carton of 10 multiple-dose vials, each vial containing a maximum of 11 doses: range 10-11 doses (0.5 mL)
NDC 80777-273-98	Carton of 10 multiple-dose vials, each vial containing a maximum of 15 doses: range 13-15 doses (0.5 mL)

During storage, minimize exposure to room light.

Store frozen between -50º to -15ºC (-58º to 5ºF). Store in the original carton to protect from light.

Do not store on dry ice or below -50ºC (-58ºF). Use of dry ice may subject vials to temperatures colder than -50°C (-58°F).

Vials may be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Do not refreeze.

Vials may be stored between 8° to 25°C (46° to 77°F) for a total of 24 hours.

After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F). Vials should be discarded 12 hours after the first puncture.

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

Transportation of Thawed Vials at 2°C to 8°C (35°F to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2° to 8°C (35° to 46°F) when shipped using

shipping containers which have been qualified to maintain 2° to 8°C (35° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2° to 8°C (35° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (35° to 46°F) until use.

20 PATIENT COUNSELING INFORMATION

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

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

21 CONTACT INFORMATION

For general questions, send an email or call the telephone number provided below.

Email	Telephone number
medinfo@modernatx.com	1-866-MODERNA (1-866-663-3762)

This EUA Prescribing Information may have been updated. For the most resent Full EUA Prescribing Information, please visit www.modernatx.com/covid19vaccine-eua.

Moderna US, Inc.
Cambridge, MA 02139

Patent(s): www.modernatx.com/patents
Revised: Mar/31/2021

Exhibit 8

Moderna: Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to ModernaTX, Inc. (Feb. 25, 2021)

U.S. FOOD & DRUG ADMINISTRATION

February 25, 2021

ModernaTX, Inc.
Attention: Ms. Carlota Vinals
200 Technology Square
Cambridge, MA 02139

Dear Ms. Vinals:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (the FD&C Act or the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 18, 2020, FDA issued an Emergency Use Authorization (EUA) for emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19 for individuals 18 years of age and older, as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Act.

On February 25, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the December 18, 2020, letter in its entirety with revisions incorporated to allow flexibility on the date of submission of monthly periodic safety reports and to revise the requirements for reporting of vaccine administration errors by ModernaTX, Inc.

Moderna COVID-19 Vaccine is for use for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The vaccine contains a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid particles. It is an investigational vaccine not licensed for any indication.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

FDA reviewed safety and efficacy data from an ongoing phase 3 trial in approximately 30,000 participants randomized 1:1 to receive Moderna COVID-19 Vaccine or saline control. The trial has enrolled participants 18 years of age and older.

FDA's review of the available safety data from 30,351 participants 18 years of age and older, who were followed for a median of 7 weeks after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. Review of additional safety data from these participants with a median of 9 weeks of follow-up after receipt of the second dose did not change FDA's assessment of safety of the vaccine.

FDA's analysis of the efficacy data from 28,207 participants 18 years of age and older without evidence of SARS-CoV-2 infection prior to dose 1 confirms the vaccine was 94.1% effective (95% confidence interval (CI) 89.3, 96.8) in preventing COVID-19 occurring at least 14 days after the second dose (with 11 COVID-19 cases in the vaccine group compared to 185 COVID-19 cases in the placebo group). In this final scheduled analysis participants had been followed for a median of 9 weeks following the second dose. This result is consistent with that obtained from an interim analysis of efficacy conducted after these participants had been followed for a median of 7 weeks after the second dose (vaccine efficacy 94.5%, 95% CI: 86.5, 97.8).

Based on the safety and effectiveness data, and review of manufacturing information regarding product quality and consistency, it is reasonable to believe that Moderna COVID-19 Vaccine may be effective. Additionally, it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Moderna COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 18 years of age and older. Finally, on December 17, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Moderna COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Moderna COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

3. There is no adequate, approved, and available alternative to the emergency use of Moderna COVID-19 Vaccine to prevent COVID-19.[3]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- ModernaTX, Inc. will supply Moderna COVID-19 Vaccine either directly or through authorized distributor(s)[4] to emergency response stakeholders[5] as directed by the U.S. government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA;
- The Moderna COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[6] and used only to prevent COVID-19 in individuals ages 18 and older; and
- The Moderna COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

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[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[4] "Authorized Distributor(s)" are identified by ModernaTX, Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Moderna COVID-19 Vaccine.

[5] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

[6] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

Product Description

The Moderna COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials.. The Moderna COVID-19 Vaccine does not contain a preservative.

Each 0.5 mL dose of the Moderna COVID-19 Vaccine contains 100 mcg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Moderna COVID-19 Vaccine also includes the following ingredients: lipids (SM-102; 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG]; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The dosing regimen is two doses of 0.5 mL each, one month apart.

The manufacture of the authorized Moderna COVID-19 Vaccine is limited to those facilities identified and agreed upon in the ModernaTX, Inc. request for authorization.

The Moderna COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Moderna COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

The Moderna COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19)

- Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 18 Years of Age and Older

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Moderna COVID-19 Vaccine, when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Moderna COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Moderna COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Moderna COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Moderna COVID-19 Vaccine is authorized to prevent COVID-19 in individuals 18 years of age and older as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

ModernaTX, Inc. and Authorized Distributor(s)

A. ModernaTX, Inc. and authorized distributor(s) will ensure that the authorized Moderna COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. ModernaTX, Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. ModernaTX, Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving authorized Moderna COVID-19 Vaccine. ModernaTX, Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. ModernaTX, Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. ModernaTX, Inc. may request changes to this authorization, including to the authorized Fact Sheets for Moderna COVID-19 Vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation[7].

F. ModernaTX, Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to ModernaTX, Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by ModernaTX, Inc.

G. ModernaTX, Inc. must submit to Investigational New Drug application (IND) number 19745 periodic safety reports at monthly intervals, in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE), beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
- Newly identified safety concerns in the interval; and
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by the Agency.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

[7] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

J. ModernaTX, Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. ModernaTX, Inc. will submit to the EUA file quarterly manufacturing reports that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report. The first report is due July 2021.

L. ModernaTX, Inc. and authorized distributor(s) will maintain records regarding release of Moderna COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. ModernaTX, Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. ModernaTX, Inc. will conduct post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Moderna COVID-19 Vaccine under this EUA in the general U.S. population (18 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. ModernaTX, Inc. will provide protocols and status update reports to the IND 19745 with agreed-upon study designs and milestone dates.

O. ModernaTX, Inc., working with its contract research organization, will continue to monitor the performance of its clinical investigators in ongoing clinical studies of its vaccine and will report to FDA promptly any significant deviations from the protocols.

Emergency Response Stakeholders

P. Emergency response stakeholders will identify vaccination sites to receive authorized Moderna COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

Q. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine

under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

R. Emergency response stakeholders receiving authorized Moderna COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

S. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

T. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose.

U. Vaccination providers administering Moderna COVID-19 Vaccine must report the following information associated with the administration of Moderna COVID-19 Vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):
- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words " Moderna COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to ModernaTX, Inc., by contacting 1-866-663-3762, by providing a copy of the VAERS form to ModernaTX, Inc., Fax: 1-866-599-1342 or by email; ModernaPV@modernatx.com.

V. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

W. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

X. Vaccination providers will ensure that any records associated with this EUA are

maintained until notified by FDA. Such records will be made available to CDC and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Moderna COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Z. All descriptive printed matter, advertising, and promotional material relating to the use of the Moderna COVID-19 Vaccine clearly and conspicuously shall state that:
- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 18 years of age and older; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

_____

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Exhibit 9

Moderna: COVID-19 Vaccine Emergency Use Authorization Review Memorandum (Dec. 18, 2020)

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	27073
Sponsor	ModernaTX, Inc.
Submission Date	November 30, 2020
Receipt Date	November 30, 2020
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Principal Discipline Reviewers from the Review Team	Sudhakar Agnihothram, Ph.D., Chair, OVRR/DVRPA; Goutam Sen, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Rachel Zhang, M.D., Clinical reviewer, OVRR/DVRPA; Ching-Long Sun, Ph.D., Toxicology reviewer, OVRR/DVRPA; Ye Yang, Ph.D., Biostatistics reviewer, OBE/DB; Alena Dabrazhynetskaya Ph.D., CMC/Product reviewer, OVRR/DVP; Li-Sheng Fowler Ph.D., CMC/Product reviewer, OVRR/DVP; Obinna Echeozo MPH, MBA, CMC/Facility reviewer; OCBQ/DMPQ; Ekaterina Allen Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Timothy Martin Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Jane Baumblatt M.D., Pharmacovigilance reviewer, OBE/DE; Daphne Stewart, Labeling reviewer, OVRR/DVRPA; Brenda Baldwin Ph.D., Data Integrity reviewer, OVRR/DVRPA; Christine Drabick M.S, BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Pharm.D., MPH, Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	December 18, 2020
Established Name/Other names used during development	Moderna COVID-19 Vaccine/mRNA-1273
Dosage Forms/Strengths and Route of Administration	A 0.5 mL Suspension for intramuscular injection
ntended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
ntended Population	Individuals 18 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA for a COVID-19 vaccine after determining that certain statutory requirements are met.

On November 30, 2020, ModernaTX (the Sponsor, also referred to as Moderna) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group) and in preventing COVID-19 following the first dose, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ≥65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group, with one severe case in the vaccine group confirmed after this analysis.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns

identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and rates and types of solicited and unsolicited adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ⩾65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Axillary swelling or tenderness of the vaccination arm (indicating presence of lymphadenopathy) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one 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 adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

Non-clinical toxicology studies with mRNA-1273, including a developmental toxicity study, did not raise specific safety concerns, and other non-clinical studies support the vaccine's immunogenicity, reduction of SARS-CoV-2 pulmonary and nasal viral load in animal challenge models, and absence of findings suggesting risk of vaccine-enhanced disease.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the

Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on December 17, 2020. Following a discussion of the data presented, the VRBPAC voted 20-1 (with 1 abstention) in favor of the determination that based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older.

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 17, 2020, meeting, the review team concludes that:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Moderna COVID-19 vaccine (mRNA-1273) may be effective to prevent such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.
- There is no adequate, approved, and available alternative to the product for preventing COVID-19 caused by SARS-CoV-2.

The review team therefore recommends issuance of an EUA for use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus

responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.3 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (the Sponsor, also referred to as Moderna) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension (-25º to -15ºC) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,400 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, Moderna submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Safety conclusions were reported by the Sponsor to be unchanged from the interim analysis. FDA considers that the totality of available data is sufficient to support an evaluation of this product for EUA.

2.4 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking

regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6] These considerations are summarized below.

Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

3. Moderna COVID-19 Vaccine (mRNA-1273)

3.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25º to -15º C (-13º to 5ºF)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the

Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

3.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

4. FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study mRNA 1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and will not be discussed in detail. Study 20-0003 is a Phase 1 open label, dose-ranging, first-in-human study of mRNA-1273 and will also not be discussed in detail.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing- vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing- Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing- Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

4.2 Study mRNA-1273-P301

4.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive

intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo (n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE=1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

Subjects who had no documented COVID-19 were censored at the last study assessment date. Subjects who discontinued the study, die due to cause unrelated to COVID-19, or were

confirmed to have COVID-19 prior to 14 days after the second dose were censored at the date of discontinuation, death, or documented COVID-19. The documented COVID-19 date was defined as the later date of: 1) the earliest systemic and/or respiratory symptoms reported, and 2) date of positive RT-PCR test, where the two dates must be within 14 days of each other.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided $\alpha = 0.025$, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition: a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38ºC), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

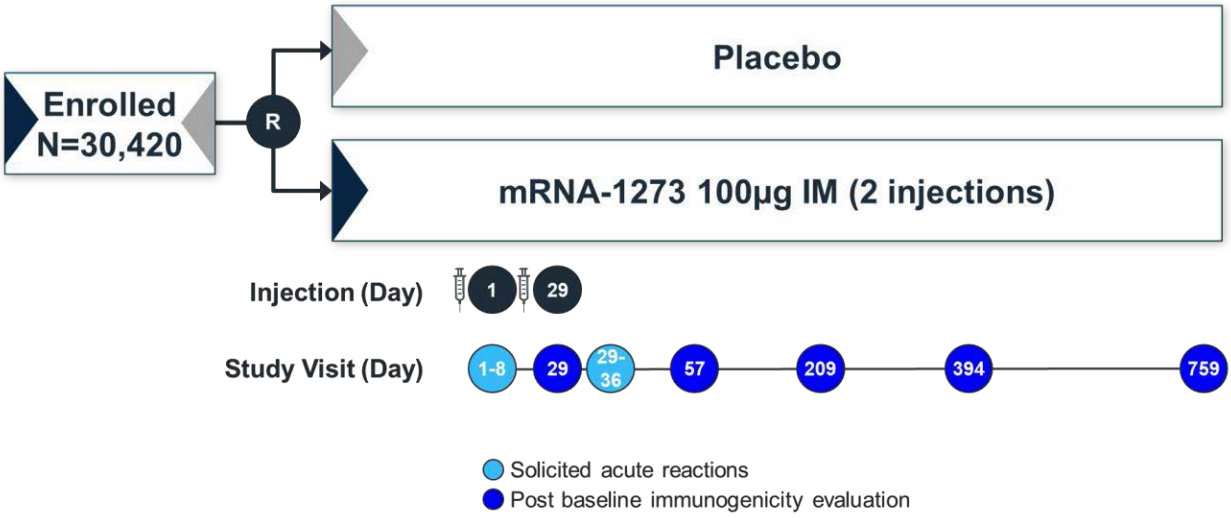
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory valuations were not assessed in Study P301 but were collected in the phase 2 Study P201.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited

adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

4.2.2 Compliance with Good Clinical Practice

As summarized in Section 5.6 (Inspections of Clinical Study Sites), Bioresearch Monitoring (BIMO) inspections were conducted at nine domestic clinical investigator sites participating in the conduct of the trial. Two of the inspections revealed deficiencies regarding the clinical investigators' conduct of the study. The deficiencies initially gave FDA cause for concern about the adequacy of the Sponsor's study monitoring. Upon further review, including consideration of additional information provided by the Sponsor, however, FDA determined that the Sponsor had a comprehensive system in place to routinely monitor compliance at all sites. FDA also determined that prior to FDA's inspections, this system was effective at independently identifying the deficiencies at the two sites, leading to implementation of corrective action plans at both sites. Following review of study-wide compliance information provided by the Sponsor that included a comprehensive and frequent monitoring plan already in place, FDA did not identify systemic concerns with trial conduct across the other study sites. The Letter of Authorization will include a condition about continued monitoring of the performance of the clinical investigators.

FDA conducted a sensitivity analysis of the primary efficacy endpoint excluding data from these sites. There was only one COVID-19 case, starting 14 days after the second dose, identified from the two sites through the November 21, 2020 efficacy data cutoff. This COVID-19 case was in a placebo recipient. The proportion of subjects enrolled at these two sites was very small relative to the overall study population, representing approximately 2.5% of the total study population. Furthermore, the sites contributed only one COVID-19 case (in the placebo group) to the primary efficacy analysis. Consequently, the study's efficacy conclusions are not materially affected by inclusion or exclusion of data from these two sites. FDA also conducted separate analyses of safety for these two sites, and in general the reported rates of solicited adverse reactions and unsolicited adverse events at these two sites were comparable to those reported in the overall safety database across study groups. Consequently, inclusion of safety data contributed by these two sites, which represent approximately 2.5% of the overall safety database (i.e., the total study population), would not materially change the conclusions of safety analyses, and their inclusion allows for the broadest possible evaluation of vaccine safety in the

trial. In light of the Sponsor's comprehensive system for identifying the deficiencies and the fact that the data from the two sites would not materially affect the safety or efficacy analyses, FDA has confidence in the data from the two sites to include the data in the overall evaluation. Therefore, FDA did not exclude the data from these two sites from either the safety or efficacy analyses presented in this review or in product labeling.

4.2.3 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

4.2.4 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study. During review of the EUA request, FDA and the Sponsor identified one additional vaccine recipient and one additional placebo recipient not accounted for in the

November 11, 2020 dataset analyses (Total Safety Set of 30,351, including 15,185 vaccine recipients and 15,166 placebo recipients). These two additional participants to not materially change the conclusions from the analyses of the November 11, 2020 safety dataset, and they are included in analyses of the November 25, 2020 dataset.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15165	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

4.2.5 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- 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)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
** High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
*** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3)
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 [a] EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. [a] EUA request (interim analysis): November 11, 2020 cutoff

4.2.6 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after dose 2. Cases were adjudicated by a blinded committee. The primary efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in

the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases /N (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases / N (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 / 13934 (<0.1) 1.840	90 / 13883 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-hazard ratio (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0047 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1

[a] EUA request (interim analysis): November 7, 2020 data cutoff.

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection

**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a] =5) N[b] (%)	Placebo (N[a] =90) N[b] (%)	Total (N[a] =95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6 / 15180	92 / 15170	93.5% (85.2, 97.2)
Positive	0 / 341	1 / 334 (0.3) 17.038	100%
Negative	6 / 14312 (<0.1) 2.154	90 / 14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0 / 527	1 / 465 (0.2)	100%

* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0 / 661	6 / 673 (0.9) 42.950	100%
Significant Cardiac Disease	0 / 686	3 / 678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1 / 901 (0.1) 5.524	11 / 884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0 / 1338	7 / 1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1 / 76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2 / 5269 (<0.1%)	46 / 5207 (0.9)	95.8% (82.6%,99.0%)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): November 07 2020 efficacy data cutoff.
* VE is calculated as 1-hazard ratio (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and represents a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

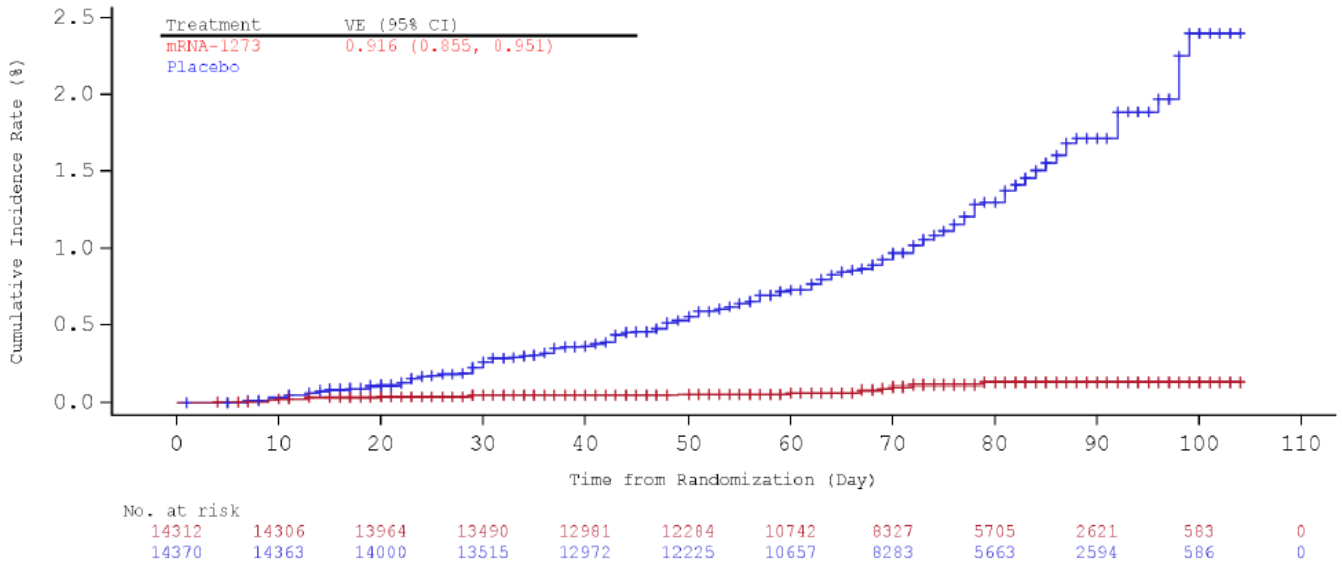
Other Secondary Efficacy Endpoints

The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Cases / N (%) Person-years of follow-up	Placebo Group N=1079 Cases / N (%) Person-years of follow-up	VE (%) (95% CI)*
After dose 1	7 / 996 (0.7) 87.5	39 / 1079 (3.6) 96.7	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5 / 996 (0.5) 38.0	11 / 1079 (1.0) 41.1	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2 / 983 (0.2) 87.2	28 / 1059 (2.6) 96.2	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-incidence rate ratio (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: Novemer 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both

participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis: EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases / N (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases / N (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 / 13934 (<0.1) 3.328	185 / 13883 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7 / 10551 (<0.1) 2.875	156 / 10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4 / 3583 (0.1); 4.595	29 / 3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1

COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.

21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).

* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

**VE and 95% CI from the stratified Cox proportional hazard model

***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%,

[1] Percentage based on number of participants in the 18 to <65 years of age group.

[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The severe COVID-19 case in a mRNA-1273 vaccine recipient described with in the discussion of the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below because it was confirmed after the analysis.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose were in the placebo group, although one severe COVID-19 occurred in the vaccine group but was not confirmed until after the analysis. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI:

89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis. The final scheduled efficacy analysis also corroborated preliminary findings of efficacy against severe COVID-19, with 30 cases in the placebo group and 0 in the vaccine group (though one severe case in the vaccine group was confirmed after the final scheduled efficacy analysis).

4.2.7 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA first independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020, followed by all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies from the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The remaining safety analyses from the November 25, 2020 cutoff date, were verified in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7

[a] There were no reports of Grade 4 injection site adverse reactions

[a] EUA request (interim analysis)-November 11, 2020

**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and axillary swelling or tenderness of the vaccination arm indicating lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary swelling or tenderness of the vaccination arm was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary swelling or tenderness was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary swelling or tenderness were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 axillary swelling or tenderness.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5%

of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary swelling or tenderness (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

The tables below present analyses of solicited local AR from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting solicited local AR are not appreciably different from those presented in the tables below.

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)
Axillary Swelling/Tenderness[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose

[a] EUA request (interim analysis)-November 11 2020

Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.

n= # of participants with specified reaction

N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

c: Axillary Swelling/Tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

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

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Axillary Swelling/Tenderness[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.

[a] EUA request (interim analysis)-November 11 2020.

Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.

n= # of participants with specified reaction

N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis

c: Axillary Swelling/Tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization

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

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 ºF). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine

recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 ºF) was reported by <0.1% (11 participants) of vaccine recipients after dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 ºF) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

The tables below present analyses of solicited systemic AR from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting solicited systemic AR are not appreciably different from those presented in the tables below.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (61.3)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ⩾39 0 – ⩽40.0°C or ⩾102.1 – ⩽104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

The tables below present analyses of unsolicited AEs from the November 11, 2020 data cutoff. FDA has examined the safety dataset from the November 25, 2020 data cutoff and verified that the proportions of subjects reporting unsolicited AEs are not appreciably different from those presented in the tables below.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): Novemer 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and

1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after

vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths in both the vaccine and placebo groups represent events and rates that occur in the general population of individuals of these ages and do not suggest a causal relationship to the vaccine.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo group than the vaccine group, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA 1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal

developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has independently verified all new deaths (including those reported through December 3, 2020) and other SAEs, and the rates and types of solicited and unsolicited AEs from the November 25, 2020 dataset. No new safety concerns have been identified. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, lymphadenopathy-related events were reported in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group, reflecting a similar imbalance in solicited axillary swelling or tenderness indicating lymphadenopathy (reported by 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively). There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one 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 adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher

than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

4.3 Study DMID Protocol 20-0003

Study Design

DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100-µg group compared to the 250-µg group, led to the selection of the 100 µg dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

4.4 Study mRNA-1273-P201

Study Design

Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who were randomized equally to receive either 2 doses of 50 µg of mRNA-1273, 100 µg of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

5. FDA Review of Other Information Submitted in Support of the EUA

5.1 Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

Moderna expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. Moderna is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered open-label mRNA-1273 vaccination and to remain in the trial, enabling Moderna to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Moderna has represented that a blinded crossover design is not feasible for them to implement, due to unwillingness of trial participants to engage in such a design, and that availability of vaccine allocated for clinical trials, which will expire soon and cannot be used under EUA, is an argument against a staged crossover approach according to EUA vaccine prioritization and availability for certain subgroups. Adverse events among those vaccinated within the open label crossover will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

5.2 Pharmacovigilance Activities

Moderna submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information. Division of Epidemiology recommendations are as follows:

1. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
    - Vaccine administration errors whether or not associated with an adverse event
    - Serious adverse events (irrespective of attribution to vaccination)
    - Cases of Multisystem Inflammatory Syndrome in adults
    - Cases of COVID-19 that result in hospitalization or death

2. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
    - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
    - Newly identified safety concerns in the interval
    - Actions taken since the last report because of adverse experiences (for example, changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

3. Moderna will conduct post-authorization observational studies for safety to evaluate the association between Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESI) along with deaths and hospitalizations, and severe COVID-19 disease. The study population should include individuals administered the authorized Moderna COVID-19 Vaccine under this EUA in the general US population, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Moderna will provide protocols and status update reports to the IND 19745 with agreed-upon study designs and milestone dates.
   The Sponsor has proposed the following three planned surveillance studies:
   - Pregnancy Cohort:
     The Sponsor plans to establish a pregnancy registry with an internal unvaccinated comparator cohort to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a full protocol for FDA review and approval prior to study start.
   - Active Follow-up for Safety:
     This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 26 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.
   - Real World Effectiveness Study:
     This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes; laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated subjects will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

   FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

4. Mandatory reporting by vaccination providers to VAERS for the following events:
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of Multisystem Inflammatory Syndrome in children and adults
   - Cases of COVID-19 that result in hospitalization or death

5. Active surveillance of vaccine recipients via the v-safe program. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

5.3 Non-Clinical Studies

Toxicology Studies

To support their EUA request, Moderna submitted the following toxicology studies:

(1) Repeat-dose toxicity study of five formulated RNA platforms encoding for viral proteins by repeated intramuscular administration to Sprague Dawley rats. Study #5002045 and 5002045 reviewed under MF19622. Study # 5002034 and 5002158 reviewed under IND 17725. Study #5002400 reviewed under IND19088. Study #5002033 reviewed under IND 17741.
(2) Repeat dose toxicity study of mRNA-1273 by intramuscular injection in Sprague Dawley rats. Study #2308-123 reviewed under IND 19745.
(3) Intramuscular combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats. Study#20248897 reviewed under IND 19745.

Based on nonclinical toxicity assessment, there were no significant safety issues to report. Two intramuscular injections of mRNA-1273 at doses up to 100 ug were well tolerated in rats. Intramuscular administrations of mRNA-1273 at dose of 100 ug to rats prior to mating and during gestation period did not reveal effects on female reproduction, fetal/embryonic development and postnatal development.

Other Non-Clinical Studies

Several nonclinical studies in mice, hamsters, and rhesus macaques were conducted to support the safety and efficacy of the mRNA-1273 COVID-19 vaccine. mRNA-1273 was assessed for immunogenicity and for protection against SARS-CoV-2 challenge in mice, hamsters, and rhesus macaques. mRNA-1273 was highly immunogenic in all species tested with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4+ response, as well as an IFNγ+, IL-2+, CD8+ T-cell response, after a single immunization. Animals immunized intramuscularly had readily detectable S-binding IgG and SARS-CoV-2 neutralizing titers (NT50) as early as one week after a single immunization, and these titers were boosted substantially with a second immunization. Immunized mice were challenged with a mouse-adapted SARS-CoV-2, and hamsters and macaques were challenged with wild-type SARS-CoV-2. The mRNA-1273 vaccine was protective in all three species as indicated by a substantial decrease in viral RNA in bronchoalveolar lavage fluid and the nasal turbinates in the immunized animals as compared with the controls. In addition, there was no histopathologic or radiographic evidence of vaccine-elicited enhanced disease in immunized animals. Based on current hypotheses regarding the etiology of vaccine-associated enhanced respiratory disease, the data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice, hamsters, and rhesus macaques; (2) the Th1 bias in T-cell responses; and (3) the reduced viral load and lack of disease markers in vaccinated animals challenged with SARS-CoV-2.

5.4 Chemistry, Manufacturing, and Control (CMC) Information

The Moderna COVID-19 vaccine (Code number mRNA-1273) is a nucleoside-modified messenger RNA (mRNA)-based vaccine indicated for active immunization for the prevention of coronavirus disease 2019.

The manufacturing process for the drug substance (DS) consists of (b) (4) The mRNA-1273 drug product (DP) is manufactured by (b) (4) filling of final containers and labeling/packaging. To support the EUA request, process performance qualification (PPQ) data and in-process, release, and characterization data for DS and DP lots were provided for each manufacturing facility. Once authorized, the Sponsor will submit the Certificates of Analysis (CoAs) of DS and DP lots to be distributed under EUA for FDA review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent scale-related changes during vaccine development to increase production capacity. DS and DP Scale A was used for the manufacture of Phase 3 clinical-trial material (CTM), while DS and DP Scale B will be used in the manufacture of vaccine intended for emergency use. An in-depth analytical comparability assessment based on a minimum of 3 DS PPQ lots and 3 DP PPQ lots at each Scale A and Scale B was performed. The submitted data show that the DS and DP lots manufactured at Scale A and Scale B are highly comparable, and the DS lots manufactured at Scale B in different facilities are also comparable. The manufacturing process and controls have been well characterized and qualified. A more comprehensive comparability assessment encompassing additional lots is ongoing and the results will be provided to the EUA upon completion of the study.
Stability studies have been designed to support the use of vaccine under the EUA. All available stability data generated using the mRNA-1273 DS and DP lots support the emergency deployment of the Moderna COVID-19 vaccine. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Stability data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of mRNA 1273 DS and DP include tests to ensure vaccine safety, identity, purity, quality, and potency. All non-compendial analytical procedures have been adequately validated. The validation results demonstrate acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the quality control of DS and DP.

The manufacture of the Moderna COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information described in the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, October 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.

- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also performed a site visit at one facility, reviewed the inspectional histories of all applicable facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Moderna COVID-19 vaccine under an Emergency Use Authorization.

5.5 Clinical Assay Information

Two diagnostic assays were used for the assessment of the Phase 3 clinical study efficacy endpoints. The Roche Elecsys Anti-SARS-CoV-2 assay was used for the evaluation of SARS-CoV-2 serostatus of study participants before vaccination. The Viracor Eurofins Clinical Diagnostics RT-qPCR was used to determine the virus infection status of study participants before vaccination and to confirm COVID-19 cases for the evaluation of clinical-study endpoints. Both assays have received FDA emergency use authorization. Additional data were submitted to support the suitability of both assays for their intended use in the Phase 3 clinical study for mRNA 1273. The Roche Elecsys Anti-SARS-CoV-2 assay is done under contract to PPD Global Central Laboratories, and the RT-qPCR assay is done by Viracor Eurofins Clinical Diagnostics. Both contracting laboratories are CAP-accredited and CLIA certified.

5.6 Inspections of Clinical Study Sites

Bioresearch Monitoring (BIMO) inspections were conducted at nine domestic clinical investigator sites participating in the conduct of study protocol mRNA-1273-P301, *A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older*. Two of the inspections revealed deficiencies regarding the clinical investigators' conduct of the study. The deficiencies initially gave FDA cause for concern about the adequacy of the Sponsor's study monitoring. Upon further review, including consideration of additional information provided by the Sponsor, however, FDA determined that the Sponsor had a comprehensive system in place to routinely monitor compliance at all sites. FDA also determined that prior to FDA's inspections, this system was effective at independently identifying the deficiencies at the two sites, leading to implementation of corrective action plans at both sites. Following review of study-wide compliance information provided by the Sponsor that included a comprehensive and frequent monitoring plan already in place, FDA did not identify systemic concerns with trial conduct across the other study sites. In light of the Sponsor's comprehensive system for monitoring compliance at all sites, FDA has confidence in the data from the sites that were not inspected. The Letter of Authorization will include a condition about continued monitoring of the performance of the clinical investigators.

5.7 EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

6.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

6.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV 2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available for ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

6.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). The trial excluded participants with known or suspected history of allergic reaction to components of the mRNA-1273 vaccine but did not exclude participants with other allergies. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. However, at the time of this review, anaphylactic reactions have been reported following administration of the Pfizer/BioNTech COVID-19 vaccine, which is based on a similar mRNA/LNP platform, during vaccination campaigns in the US and UK. Two of these reports (both in the UK) were in individuals with prior history of severe/anaphylactic reactions to food or drug allergens that are not components of the vaccine. In the US, two individuals without known history of allergic reactions experienced anaphylaxis within minutes after vaccination, one resulting in hospitalization, and several apparently less severe immediate hypersensitivity reactions have also been reported. All of these events were treated with appropriate medical interventions, and none were fatal. Investigation into these events and the potential for mRNA/LNP vaccines to cause severe allergic/anaphylactic reactions is ongoing. The prescribing information and fact sheets for use of mRNA-1273 under EUA will describe the need for post-vaccination monitoring for severe immediate hypersensitivity or anaphylactic reactions and need for facilities where vaccinations are being conducted to have medical treatment immediately available to respond to such reactions. Additionally, surveillance for allergic reactions, including severe or anaphylactic reactions, following vaccination with mRNA-1273 will proceed through established mechanisms (e.g., mandatory reporting of AEs to VAERS by vaccine providers) and investigated rapidly through joint efforts by CDC and FDA.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

6.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA 1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Meeting Summary

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on December 17, 2020, to discuss Moderna's EUA request. The meeting agenda included: an overview by FDA on EUA and considerations specific to COVID-19 vaccines; a presentation on conduct of placebo-controlled studies in the event that a vaccine becomes available under EUA; presentation of data from studies of the Moderna COVID-19 Vaccine by representatives of Moderna; a public comment period; an FDA presentation of its independent review of the data submitted in support of the EUA request; and a discussion and vote by the VRBPAC.

The VRBPAC was asked to discuss the following items, with no vote:

In considering Moderna's plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in:

- Ongoing clinical trials with the Moderna COVID-19 vaccine
- Other studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine

Regarding critical data to be obtained in ongoing trials with the Moderna COVID-19 vaccine, committee members discussed the importance of collecting blood specimens obtained from breakthrough cases to evaluate T- and B- cell immunity and to identify correlates of protection, and the importance of collecting respiratory specimens obtained from breakthrough cases to evaluate effect of the vaccine on shedding of infectious virus and to provide information about potential antigenic escape mutants. Members commented that efforts should be made to obtain data on long term safety of the vaccine, waning of immunity, the vaccine's impact on virus transmission, and asymptomatic infection. In addition, they suggested that ongoing studies should collect additional data on vaccine effectiveness in subjects at increased risk for COVID-19, pregnant women and pediatric populations.

Committee members were asked to discuss whether the ongoing Phase 3 trial should be continued using a blinded cross-over design or an open-label design as proposed by Moderna. Some members stressed the importance of using a blinded cross-over design in order to preserve data integrity and to allow an evaluation of waning of immunity and duration of protection. Other members opined that even though a blinded cross-over design would be ideal, it would present with logistical challenges, and that high drop-out rates can be anticipated because clinical trial participants would obtain a vaccine made available under EUA before a blinded cross-over could be implemented. Therefore, open-label unblinded vaccination of placebo recipients, even though not ideal, may be a more realistic option. However, to preserve blinded placebo-controlled follow-up for as long as is practical, some committee members opined that placebo recipients should be offered the vaccine as they become eligible for vaccination according to CDC prioritization groups.

The committee suggested for the following data to be obtained in additional studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine: data on vaccine effectiveness in the elderly, immunogenicity data from dose ranging studies, in particular in immunocompromised subpopulations, effectiveness of the vaccine following one dose, and interchangeability of the two COVID-19 mRNA vaccines. Additional studies should be conducted to obtain data regarding duration of protection, to identify a correlate of protection, to further evaluate Bell's palsy as an adverse event as well as to evaluate other neurological and cardiac outcomes (both in terms of vaccine safety and effect of vaccination on prevention of these outcomes when related to COVID-19), co-administration with other vaccines, and vaccine safety and effectiveness in pregnant and pediatric subjects.

Following this discussion, the VRBPAC was asked to vote on whether, based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The results of the vote were as follows: Yes = 20, No = 0, Abstain = 1. Thus, the committee voted in favor of a determination that based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older.

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the December 17, 2020 meeting, the review team concludes that:

- As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, it is reasonable to believe that the Moderna COVID-19 vaccine (mRNA-1273) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2. In the final scheduled primary efficacy analysis of PCR-confirmed and adjudicated COVID-19 cases in an ongoing randomized, blinded, placebo-controlled Phase 3 clinical trial, vaccine efficacy after 14 days post dose 2 was 94.1% (95% CI 89.3%, 96.8%). Efficacy outcomes were high across demographic subgroups and in participants with medical comorbidities associated with higher risk of severe COVID-19. A secondary efficacy analysis using a more severe COVID-19 case definition included 30 adjudicated cases in the placebo group and none in the vaccine group (though one severe case in the vaccine group was confirmed after this analysis). Additional post-hoc efficacy analyses also suggested efficacy against COVID-19 in the time period between dose 1 and dose 2.

- Based on the data summarized in Sections 4 and 5 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 14 days after dose 2, reduction in the risk of confirmed COVID-19 after dose 1 and before dose 2, and reduction in the risk of confirmed severe COVID-19 any time after dose 1. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up (including further evaluation of risk of Bell's palsy and severe allergic/anaphylactic reactions following vaccination), risks associated with vaccination of specific populations such as children younger than 18 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, and available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The review team therefore recommends issuance of an EUA for use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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Exhibit 10

Janssen: Fact Sheet for Recipients and Caregivers (Apr. 23, 2021 (revised))

FACT SHEET FOR RECIPIENTS AND CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF THE JANSSEN COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19) IN INDIVIDUALS 18 YEARS OF AGE AND OLDER

You are being offered the Janssen COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of receiving the Janssen COVID-19 Vaccine, which you may receive because there is currently a pandemic of COVID-19.

The Janssen COVID-19 Vaccine may prevent you from getting COVID-19. There is no U.S. Food and Drug Administration (FDA) approved vaccine to prevent COVID-19.

Read this Fact Sheet for information about the Janssen COVID-19 Vaccine. Talk to the vaccination provider if you have questions. It is your choice to receive the Janssen COVID-19 Vaccine.

The Janssen COVID-19 Vaccine is administered as a **single dose**, into the muscle.

The Janssen COVID-19 Vaccine may not protect everyone.

This Fact Sheet may have been updated. For the most recent Fact Sheet, please visit www.janssencovid19vaccine.com.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?

COVID-19 is caused by a coronavirus called SARS-CoV-2. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Common 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.

WHAT IS THE JANSSEN COVID-19 VACCINE?

The Janssen COVID-19 Vaccine is an unapproved vaccine that may prevent COVID-19. There is no FDA-approved vaccine to prevent COVID-19.

The FDA has authorized the emergency use of the Janssen COVID-19 Vaccine to prevent COVID-19 in individuals 18 years of age and older under an Emergency Use Authorization (EUA).

For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE JANSSEN COVID-19 VACCINE?

Tell the vaccination provider about all of your medical conditions, including if you:

- have any allergies,
- have a fever,
- have a bleeding disorder or are on a blood thinner,
- are immunocompromised or are on a medicine that affects your immune system,
- are pregnant or plan to become pregnant,
- are breastfeeding,
- have received another COVID-19 vaccine,

WHO SHOULD GET THE JANSSEN COVID-19 VACCINE?

FDA has authorized the emergency use of the Janssen COVID-19 Vaccine in individuals 18 years of age and older.

WHO SHOULD NOT GET THE JANSSEN COVID-19 VACCINE?

You should not get the Janssen COVID-19 Vaccine if you:

- had a severe allergic reaction to any ingredient of this vaccine.

WHAT ARE THE INGREDIENTS IN THE JANSSEN COVID-19 VACCINE?

The Janssen COVID-19 Vaccine includes the following ingredients: recombinant, replication-incompetent adenovirus type 26 expressing the SARS-CoV-2 spike protein, citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate-80, sodium chloride.

HOW IS THE JANSSEN COVID -19 VACCINE GIVEN?

The Janssen COVID-19 Vaccine will be given to you as an injection into the muscle.

The Janssen COVID-19 Vaccine vaccination schedule is a **single dose**.

HAS THE JANSSEN COVID-19 VACCINE BEEN USED BEFORE?

The Janssen COVID-19 Vaccine is an unapproved vaccine. In an ongoing clinical trial, 21,895 individuals 18 years of age and older have received the Janssen COVID-19 Vaccine.

WHAT ARE THE BENEFITS OF THE JANSSEN COVID-19 VACCINE?

In an ongoing clinical trial, the Janssen COVID-19 Vaccine has been shown to prevent COVID-19 following a single dose. The duration of protection against COVID-19 is currently unknown.

WHAT ARE THE RISKS OF THE JANSSEN COVID-19 VACCINE?

Side effects that have been reported with the Janssen COVID-19 Vaccine include:

- Injection site reactions: pain, redness of the skin and swelling.
- General side effects: headache, feeling very tired, muscle aches, nausea, and fever.

There is a remote chance that the Janssen COVID-19 Vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the Janssen COVID-19 Vaccine. For this reason, your vaccination provider may ask you to stay at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing,
- Swelling of your face and throat,
- A fast heartbeat,
- A bad rash all over your body,
- Dizziness and weakness.

Blood clots involving blood vessels in the brain, abdomen, and legs along with low levels of platelets (blood cells that help your body stop bleeding), have occurred in some people who have received the Janssen COVID-19 Vaccine. In people who developed these blood clots and low levels of platelets, symptoms began approximately one to two-weeks following vaccination. Most people who developed these blood clots and low levels of platelets were females ages 18 through 49 years. The chance of having this occur is remote. You should seek medical attention right away if you have any of the following symptoms after receiving Janssen COVID-19 Vaccine:

- Shortness of breath,
- Chest pain,
- Leg swelling,
- Persistent abdominal pain,
- Severe or persistent headaches or blurred vision,
- Easy bruising or tiny blood spots under the skin beyond the site of the injection.

These may not be all the possible side effects of the Janssen COVID-19 Vaccine. Serious and unexpected effects may occur. The Janssen COVID-19 Vaccine is still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?

If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Call the vaccination provider or your healthcare provider if you have any side effects that bother you or do not go away.

Report vaccine side effects to **FDA/CDC Vaccine Adverse Event Reporting System (VAERS)**. The VAERS toll-free number is 1-800-822-7967 or report online to https://vaers.hhs.gov/reportevent.html. Please include "Janssen COVID-19 Vaccine EUA" in the first line of box #18 of the report form.

In addition, you can report side effects to Janssen Biotech, Inc. at the contact information provided below.

e-mail	Fax number	Telephone numbers
JNJvaccineAE@its.jnj.com	215-293-9955	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

You may also be given an option to enroll in **v-safe**. **V-safe** is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. **V-safe** asks questions that help CDC monitor the safety of COVID-19 vaccines. **V-safe** also provides live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information on how to sign up, visit: www.cdc.gov/vsafe.

WHAT IF I DECIDE NOT TO GET THE JANSSEN COVID-19 VACCINE?

It is your choice to receive or not receive the Janssen COVID-19 Vaccine. Should you decide not to receive it, it will not change your standard medical care.

ARE OTHER CHOICES AVAILABLE FOR PREVENTING COVID-19 BESIDES JANSSEN COVID-19 VACCINE?

Currently, there is no FDA approved alternative vaccine available for prevention of COVID-19. Other vaccines to prevent COVID-19 may be available under Emergency Use Authorization.

CAN I RECEIVE THE JANSSEN COVID-19 VACCINE WITH OTHER VACCINES?

There is no information on the use of the Janssen COVID-19 Vaccine with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?

If you are pregnant or breastfeeding, discuss your options with your healthcare provider.

WILL THE JANSSEN COVID-19 VACCINE GIVE ME COVID-19?

No. The Janssen COVID-19 Vaccine does not contain SARS-CoV-2 and cannot give you COVID-19.

KEEP YOUR VACCINATION CARD

When you receive the Janssen COVID-19 Vaccine, you will get a vaccination card to document the name of the vaccine and date of when you received the vaccine.

ADDITIONAL INFORMATION

If you have questions or to access the most recent Janssen COVID-19 Vaccine Fact Sheets, scan the QR code using your device, visit the website or call the telephone numbers provided below.

QR Code	Fact Sheets Website	Telephone numbers
	www.janssencovid19vaccine.com.	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

HOW CAN I LEARN MORE?

- Ask the vaccination provider.
- Visit CDC at https://www.cdc.gov/coronavirus/2019-ncov/index.html.
- Visit FDA at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

Contact your local or state public health department.

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?

The vaccination provider may include your vaccination information in your state/local jurisdiction's Immunization Information System (IIS) or other designated system. For more information about IISs visit: https://www.cdc.gov/vaccines/programs/iis/about.html.

CAN I BE CHARGED AN ADMINISTRATION FEE FOR RECEIPT OF THE COVID-19 VACCINE?

No. At this time, the provider cannot charge you for a vaccine dose and you cannot be charged an out-of-pocket vaccine administration fee or any other fee if only receiving a COVID-19 vaccination. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients).

WHERE CAN I REPORT CASES OF SUSPECTED FRAUD?

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

WHAT IS THE COUNTERMEASURE INJURY COMPENSATION PROGRAM?

The Countermeasures Injury Compensation Program (CICP) is a federal program that may help pay for costs of medical care and other specific expenses for certain people who have been seriously injured by certain medicines or vaccines, including this vaccine. Generally, a claim must be submitted to the CICP within one (1) year from the date of receiving the vaccine. To learn more about this program, visit www.hrsa.gov/cicp or call 1-855-266-2427.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?

The United States FDA has made the Janssen COVID-19 Vaccine available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

The Janssen COVID-19 Vaccine has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that the product may be effective to prevent COVID-19 during the COVID-19 pandemic and that the known and potential benefits of the product outweigh the known and potential risks of the product. All of these criteria must be met to allow for the product to be used during the COVID-19 pandemic.

The EUA for the Janssen COVID-19 Vaccine is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

Manufactured by:
Janssen Biotech, Inc.
a Janssen Pharmaceutical Company of Johnson & Johnson
Horsham, PA 19044, USA

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

For more information, call US Toll Free: 1-800-565-4008, US Toll: (908) 455-9922 or go to www.janssencovid19vaccine.com

Revised: Apr/23/2021

Scan to capture that this Fact Sheet was provided to vaccine recipient for the electronic medical records/immunization information systems.

Barcode Date: 02/2021

Exhibit 11

Janssen: Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) (Apr. 23, 2021 (revised))

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE JANSSEN COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, Janssen COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

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 Multisystem Inflammatory Syndrome (MIS) in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Janssen COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR THE JANSSEN COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Janssen COVID-19 Vaccine is a suspension for intramuscular injection administered as a **single dose** (0.5 mL).

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.janssencovid19vaccine.com.

For information on clinical trials that are testing the use of the Janssen COVID-19 Vaccine for active immunization against 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 and handling information in this Fact Sheet supersedes the storage and handling information on the carton and vial labels.

Storage and Handling

Storage Prior to First Puncture of the Vaccine Vial

Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.

Revised: Apr/23/2021

Unpunctured vials of Janssen COVID-19 Vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours.

The Janssen COVID-19 Vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 2 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.

Storage After First Puncture of the Vaccine Vial

After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard the vial if vaccine is not used within these times.

Dosing and Schedule

The Janssen COVID-19 Vaccine is administered intramuscularly as a **single dose** (0.5 mL).

There are no data available on the use of the Janssen COVID-19 Vaccine to complete a vaccination series initiated with another COVID-19 Vaccine.

Dose Preparation

- The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. Visually inspect the Janssen COVID-19 Vaccine vials for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer the vaccine.
- Before withdrawing each dose of vaccine, carefully mix the contents of the multi-dose vial by swirling gently in an upright position for 10 seconds. **Do not shake**.
- Each dose is 0.5 mL. Each vial contains five doses. Do not pool excess vaccine from multiple vials.
- The Janssen COVID-19 Vaccine does not contain a preservative. Record the date and time of first use on the Janssen COVID-19 Vaccine vial label. After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard if vaccine is not used within these times.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Revised: Apr/23/2021

Administer the Janssen COVID-19 Vaccine intramuscularly.

CONTRAINDICATION

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

WARNINGS

Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Janssen COVID-19 Vaccine.

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

Thrombosis with Thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia. In individuals with suspected thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. The American Society of Hematology has published considerations relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine (*https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia*). (*see Full EUA Prescribing Information*).

Altered Immunocompetence

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

Limitations of Vaccine Effectiveness

The Janssen COVID-19 Vaccine may not protect all vaccinated individuals.

ADVERSE REACTIONS

Adverse reactions reported in a clinical trial following administration of the Janssen COVID-19 Vaccine include injection site pain, headache, fatigue, myalgia, nausea, fever, injection site erythema and injection site swelling. In clinical studies, severe allergic reactions, including

anaphylaxis, have been reported following the administration of the Janssen COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Janssen COVID-19 Vaccine.

USE WITH OTHER VACCINES

There is no information on the co-administration of the Janssen COVID-19 Vaccine 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 "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.janssencovid19vaccine.com to obtain the Fact Sheet) prior to the individual receiving the Janssen COVID-19 Vaccine, including:

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

For information on clinical trials that are testing the use of the Janssen COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the name of the vaccine ("Janssen COVID-19 Vaccine") and date of administration to document vaccination.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR JANSSEN COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of the Janssen COVID-19 Vaccine, the following items are required. Use of

unapproved Janssen COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements must be met):

1. The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Janssen COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving the Janssen COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

   - vaccine administration errors whether or not associated with an adverse event,
   - serious adverse events* (irrespective of attribution to vaccination),
   - cases of Multisystem Inflammatory Syndrome (MIS) in adults, and
   - cases of COVID-19 that result in hospitalization or death.

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words "Janssen COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults, and cases of COVID-19 that result in hospitalization or death following administration of the Janssen COVID-19 Vaccine to recipients.

   * 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 one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND JANSSEN BIOTECH, INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

Revised: Apr/23/2021

To the extent feasible, report adverse events to Janssen Biotech, Inc. using the contact information below or by providing a copy of the VAERS form to Janssen Biotech, Inc:

e-mail	Fax number	Telephone numbers
JNJvaccineAE@its.jnj.com	215-293-9955	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

ADDITIONAL INFORMATION

For general questions or to access the most recent Janssen COVID-19 Vaccine Fact Sheets, scan the QR code using your device, visit www.janssencovid19vaccine.com or call the telephone numbers provided below.

QR Code	Fact Sheets Website	Telephone numbers
	www.janssencovid19vaccine.com.	US Toll Free: 1-800-565-4008 US Toll: 1-908-455-9922

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

FEDERAL COVID-19 VACCINATION PROGRAM

This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, HRSA COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see *https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html*.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or TIPS.HHS.GOV.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) 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, Janssen COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 18 years of age and older.

Revised: Apr/23/2021

FDA issued this EUA, based on Janssen Biotech, Inc.'s request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Janssen COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the Full EUA Prescribing Information.

This EUA for the Janssen COVID-19 Vaccine 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.

THE COUNTERMEASURES INJURY COMPENSATION PROGRAM

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by:
Janssen Biotech, Inc.
a Janssen Pharmaceutical Company of Johnson & Johnson
Horsham, PA 19044, USA

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

Revised: Apr/23/2021

Revised: Apr/23/2021

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION JANSSEN COVID-19 VACCINE

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

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

Revised: Apr/23/2021

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Janssen COVID-19 vaccine 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 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

- The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. Visually inspect the Janssen COVID-19 Vaccine vials for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer the vaccine.
- Before withdrawing each dose of vaccine, carefully mix the contents of the multi-dose vial by swirling gently in an upright position for 10 seconds. **Do not shake**.
- Each dose is 0.5 mL. Each vial contains five doses. Do not pool excess vaccine from multiple vials.
- The Janssen COVID-19 Vaccine does not contain a preservative. Record the date and time of first use on the Janssen COVID-19 Vaccine vial label. After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard if vaccine is not used within these times.

2.2 Administration

Visually inspect each dose in the dosing syringe prior to administration. The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent suspension. During the visual inspection,

- verify the final dosing volume of 0.5 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Janssen COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule

The Janssen COVID-19 Vaccine is administered intramuscularly as a **single dose** (0.5 mL).

There are no data available on the use of the Janssen COVID-19 Vaccine to complete a vaccination series initiated with another COVID-19 Vaccine.

3 DOSAGE FORMS AND STRENGTHS

Janssen COVID-19 Vaccine is a suspension for intramuscular injection. A single dose is 0.5 mL.

4 CONTRAINDICATIONS

Do not administer the Janssen COVID-19 Vaccine to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the Janssen COVID-19 Vaccine *[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 the Janssen COVID-19 Vaccine.

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

5.2 Thrombosis with Thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination *[see Overall Safety Summary (6.2)]*. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal. Specific risk factors for thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine and the level of potential excess risk due to vaccination are under investigation. Based on currently available evidence, a causal relationship between thrombosis with thrombocytopenia and the Janssen COVID-19 Vaccine is plausible.

Healthcare professionals should be alert to the signs and symptoms of thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine. The clinical course shares features with autoimmune heparin-induced thrombocytopenia. In individuals with suspected thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. The American Society of Hematology has published considerations relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine (*https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia*).

Recipients of Janssen COVID-19 Vaccine should be instructed to seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, persistent abdominal pain,

neurological symptoms (including severe or persistent headaches or blurred vision), or petechiae beyond the site of vaccination.

5.3 Altered Immunocompetence

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

5.4 Limitations of Vaccine Effectiveness

The Janssen COVID-19 Vaccine may not protect all vaccinated individuals.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults, and hospitalized or fatal cases of COVID-19 following vaccination with the Janssen COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Janssen Biotech, Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS or Janssen Biotech, Inc.

In study COV3001, the most common local solicited adverse reaction (≥10%) reported was injection site pain (48.6%). The most common systemic adverse reactions (≥10%) were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%) (see Tables 1 to 4).

Severe allergic reactions, including one case of anaphylaxis in an ongoing open-label study in South Africa, have been reported following the Janssen COVID-19 vaccine administered in clinical studies.

Thrombosis involving large blood vessels, including the cerebral venous sinuses, portal vein, lower extremity veins, and pulmonary artery, with thrombocytopenia have been reported following the Janssen 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.

The safety of the Janssen COVID-19 Vaccine has been assessed in an ongoing Phase 3 Study (COV3001). A total of 43,783 individuals were enrolled in this study, of whom 21,895 adults aged 18 years and older received the Janssen COVID-19 Vaccine [Full Analysis Set (FAS)]. This study is being conducted in the United States (n=19,302), Brazil (n=7,278), South Africa (n=6,576), Colombia (n=4,248), Argentina (n=2,996), Peru (n=1,771), Chile (n=1,133), Mexico (n=479). In this study, 45.0% were female, 54.9% were male, 58.7% were White, 19.4% were Black or African American, 45.3% were Hispanic or Latino, 3.3% were Asian, 9.5% were American Indian/Alaska Native and 0.2% were Native Hawaiian or other Pacific Islander, 5.6% were from multiple racial groups and 1.4% were unknown races (see Table 5). The median age of individuals was 52.0 years

(range: 18-100). There were 4,217 (9.6%) individuals who were SARS-CoV-2 seropositive at baseline and who were included in the study. In the United States, 838 of 19,302 (4.3%) individuals were SARS-CoV-2 seropositive. Demographic characteristics were similar among individuals who received the Janssen COVID-19 Vaccine and those who received saline placebo.

The safety subset includes 6,736 individuals (3,356 from the Janssen COVID-19 Vaccine group, 3,380 from the placebo group). The demographic profile in the safety subset was similar in terms of age and gender compared to the FAS. A larger percentage of individuals in the safety subset were White (83.4%) compared to the FAS (58.7%). Geographically, the safety subset was limited to individuals from the United States (51.4%), Brazil (38.5%) and South Africa (10.2%). Fewer individuals in the safety subset compared to the FAS were SARS-CoV-2 seropositive at baseline, 4.5% vs. 9.6%, and had at least one comorbidity 34.1% vs 40.8%.

Safety monitoring in the clinical study consisted of monitoring for: (1) solicited local and systemic reactions occurring in the 7 days following vaccination in a subset of individuals (safety subset), (2) unsolicited adverse events (AEs) occurring in the 28 days following vaccination in the safety subset, (3) medically-attended AEs (MAAEs) occurring in the 6 months following vaccination in the entire study population (FAS), (4) serious AEs (SAEs) and AEs leading to study discontinuation for the duration of the study in the entire study population.

Solicited adverse reactions

Shown below are the frequencies of solicited local adverse reactions (Tables 1 and 2) and systemic adverse reactions (Tables 3 and 4) reported in adults by age group in the ongoing Phase 3 clinical trial (COV3001) in the 7 days following vaccination.

Table 1: Solicited Local Adverse Reactions Reported in the 7 Days Following Vaccination - Individuals 18 to 59 Years of Age

Adverse Reactions	Janssen COVID-19 Vaccine N=2,036 n(%)	Placebo N=2,049 n(%)
Injection Site Pain		
Any	1,193 (58.6)	357 (17.4)
Grade 3[a]	8 (0.4)	0
Injection Site Erythema		
Any (≥25 mm)	184 (9.0)	89 (4.3)
Grade 3[b]	6 (0.3)	2 (0.1)
Injection Site Swelling		
Any (≥25 mm)	142 (7.0)	32 (1.6)
Grade 3[b]	5 (0.2)	2 (0.1)

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 2: Solicited Local Adverse Reactions Reported in the 7 Days Following Vaccination - Individuals 60 Years of Age and Older

Adverse Reactions	Janssen COVID-19 Vaccine N=1,320 n(%)	Placebo N=1,331 n(%)
Injection Site Pain		
Any	439 (33.3)	207 (15.6)
Grade 3[a]	3 (0.2)	2 (0.2)

Injection Site Erythema		
Any (≥25 mm)	61 (4.6)	42 (3.2)
Grade 3[b]	1 (0.1)	0
Injection Site Swelling		
Any (≥25 mm)	36 (2.7)	21 (1.6)
Grade 3[b]	2 (0.2)	0

[a] Grade 3 injection site pain: Defined as incapacitating symptoms; inability to do work, school, or usual activities; use of narcotic pain reliever.

[b] Grade 3 injection site swelling and erythema: Defined as >100 mm.

Table 3: Solicited Systemic Adverse Reactions Reported in the 7 Days Following Vaccination - Individuals 18 to 59 Years of Age

Adverse Reactions	Janssen COVID-19 Vaccine N=2,036 n(%)	Placebo N=2,049 n(%)
Headache		
Any	905 (44.4)	508 (24.8)
Grade 3[a]	18 (0.9)	5 (0.2)
Fatigue		
Any	891 (43.8)	451 (22.0)
Grade 3[b]	25 (1.2)	4 (0.2)
Myalgia		
Any	796 (39.1)	248 (12.1)
Grade 3[b]	29 (1.4)	1 (<0.1)
Nausea		
Any	315 (15.5)	183 (8.9)
Grade 3[b]	3 (0.1)	3 (0.1)
Fever[c]		
Any	261 (12.8)	14 (0.7)
Grade 3	7 (0.3)	0
Use of antipyretic or pain medication	538 (26.4)	123 (6.0)

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38 C/100.4 F. Grade 3 fever: Defined as 39.0 C - 40.0 C (102.1 F - 104.0 F).

Table 4: Solicited Systemic Adverse Reactions Reported in the 7 Days Following Vaccination - Individuals 60 Years of Age and Older

Adverse Reactions	Janssen COVID-19 Vaccine N=1,320 n(%)	Placebo N=1,331 n(%)
Headache		
Any	401 (30.4)	294 (22.1)
Grade 3[a]	5 (0.4)	4 (0.3)
Fatigue		
Any	392 (29.7)	277 (20.8)
Grade 3[b]	10 (0.8)	5 (0.4)
Myalgia		
Any	317 (24.0)	182 (13.7)
Grade 3[b]	3 (0.2)	5 (0.4)
Nausea		
Any	162 (12.3)	144 (10.8)
Grade 3[b]	3 (0.2)	3 (0.2)
Fever[c]		
Any	41 (3.1)	6 (0.5)
Grade 3	1 (0.1)	0

Use of antipyretic or pain medication	130 (9.8)	68 (5.1)

[a] Grade 3 headache: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever

[b] Grade 3 fatigue, myalgia, nausea: Defined as incapacitating symptoms; requires bed rest and/or results in loss of work, school, or cancellation of social activities; use of narcotic pain reliever.

[c] Fever of any grade: Defined as body temperature ≥38 C/100.4 F. Grade 3 fever: Defined as 39.0 C - 40.0 C (102.1 F - 104.0 F).

Solicited local and systemic adverse reactions reported following administration of the Janssen COVID-19 Vaccine had a median duration of 1 to 2 days.

Unsolicited adverse events

Individuals within the safety subset in study COV3001 (N=6,736) were monitored for unsolicited adverse events (AEs) for 28 days following vaccination with 99.9% (N= 6,730) of individuals completing the full 28 days of follow-up. The proportion of individuals who reported one or more unsolicited AEs was similar among those in the Janssen COVID-19 Vaccine group (13.1%) and those in the placebo group (12.0%).

Serious Adverse Events (SAEs) and other events of interest

In study COV3001, up to a cut-off date of January 22, 2021, 54.6% of individuals had follow-up duration of 8 weeks. The median follow-up duration for all individuals was 58 days. SAEs, excluding those related to confirmed COVID-19, were reported by 0.4% (n=83) of individuals who received the Janssen COVID-19 Vaccine (N= 21,895) and 0.4% (n=96) of individuals who received placebo (N= 21,888).

Additional adverse events of interest, including but not limited to allergic, neurologic, inflammatory, vascular, and autoimmune disorders, were analyzed among all adverse events collected through protocol-specified safety monitoring procedures as well as unsolicited reporting.

Urticaria (all non-serious) was reported in five vaccinated individuals and 1 individual who received placebo in the 7 days following vaccination. In addition, an SAE of hypersensitivity, not classified as anaphylaxis, was reported in 1 vaccinated individual with urticaria beginning two days following vaccination and angioedema of the lips with no respiratory distress beginning four days following vaccination. The event was likely related to the vaccine.

An SAE of severe pain in the injected arm, not responsive to analgesics, with immediate onset at time of vaccination, and that was ongoing 74 days following vaccination was reported in an individual who received the Janssen COVID-19 Vaccine. An SAE of severe generalized weakness, fever, and headache, with onset on the day following vaccination and resolution three days following vaccination was reported in an individual who received the Janssen COVID-19 Vaccine. Both SAEs are likely related to the vaccine.

Numerical imbalances, with more events in vaccine than placebo recipients, were observed for the following serious and other adverse events of interest in individuals receiving the vaccine or placebo, respectively:

- Thromboembolic events:
    - Deep vein thrombosis: 6 events (2 serious; 5 within 28 days of vaccination) vs. 2 events (1 serious; 2 within 28 days of vaccination).
    - Pulmonary embolism: 4 events (3 serious; 2 within 28 days of vaccination) vs. 1 event (serious and within 28 days of vaccination).
    - Transverse sinus thrombosis with thrombocytopenia: 1 event (serious, with onset of symptoms 8 days post-vaccination) vs. 0.
- Seizures: 4 events (1 serious; 4 within 28 days of vaccination) vs. 1 event (0 serious and 0 within 28 days following vaccination).
- Tinnitus: 6 events (0 serious; 6 within 28 days of vaccination, including 3 within 2 days of vaccination) vs. 0.

For these events, a causal relationship with the Janssen COVID-19 vaccine could not be determined based on study COV3001. The assessment of causality was confounded by the presence of underlying medical conditions that may have predisposed individuals to these events. However, taking into consideration post-authorization experience, a causal relationship with Janssen COVID-19 Vaccine is plausible for thrombosis with thrombocytopenia [*see Warnings and Precautions (5.2) and Overall Safety Summary (6.2)]*.

There were no additional notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and cardiovascular events) that would suggest a causal relationship to the Janssen COVID-19 Vaccine.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post-authorization use of the Janssen COVID-19 Vaccine.

Thrombosis involving large blood vessels, including the cerebral venous sinuses, portal vein, lower extremity veins, and pulmonary artery, combined with thrombocytopenia *[see Warnings and Precautions (5.2)]*.

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 Janssen COVID-19 Vaccine administration to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event,
- Serious adverse events* (irrespective of attribution to vaccination),
- Cases of Multisystem Inflammatory Syndrome (MIS) in 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 one of the outcomes listed above.

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, 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 Janssen COVID-19 vaccine,
- 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.

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

1. In Box 17, provide information on Janssen COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.

2. In Box 18, description of the event:

    a. Write "Janssen COVID-19 Vaccine 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).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Janssen Biotech, Inc. using the contact information below or by providing a copy of the VAERS form to Janssen Biotech, Inc:

e-mail	Fax number	Telephone numbers
JNJvaccineAE@its.jnj.com	215-293-9955	US Toll Free: 1-800-565-4008 US Toll: (908) 455-9922

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Janssen COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Janssen COVID-19 Vaccine during pregnancy. Women who are vaccinated with Janssen COVID-

19 Vaccine during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com.

Risk Summary

All Pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. 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 Janssen COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive developmental toxicity study female rabbits were administered 1 mL of the Janssen COVID-19 Vaccine (a single human dose is 0.5 mL) by intramuscular injection 7 days prior to mating and on Gestation Days 6 and 20 (i.e., one vaccination during early and late gestation, respectively). No vaccine related adverse effects on female fertility, embryo-fetal or postnatal development up to Postnatal Day 28 were observed.

11.2 Lactation

Risk Summary

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

11.3 Pediatric Use

Emergency Use Authorization of the Janssen COVID-19 Vaccine does not include use in individuals younger than 18 years of age.

11.4 Geriatric Use

Clinical studies of Janssen COVID-19 Vaccine included individuals 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18)]*. Of the 21,895 individuals who received a single-dose of the Janssen COVID-19 Vaccine in COV3001, 19.5% (n=4,259) were 65 years of age and older and 3.7% (n=809) were 75 years of age and older. No overall differences in safety or efficacy were observed between individuals 65 years of age and older and younger individuals.

13 DESCRIPTION

The Janssen COVID-19 Vaccine is a colorless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection. It contains no visible particulates. The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation.

The Ad26 vector expressing the SARS-CoV-2 S protein is grown in PER.C6 TetR cells, in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is

processed through several purification steps, formulated with inactive ingredients and filled into vials.

Each 0.5 mL dose of Janssen COVID-19 Vaccine is formulated to contain 5×10^{10} virus particles (VP) and the following inactive ingredients: citric acid monohydrate (0.14 mg), trisodium citrate dihydrate (2.02 mg), ethanol (2.04 mg), 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg), polysorbate-80 (0.16 mg), sodium chloride (2.19 mg). Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng).

Janssen COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The Janssen COVID-19 Vaccine is composed of a recombinant, replication-incompetent human adenovirus type 26 vector that, after entering human cells, expresses the SARS-CoV-2 spike (S) antigen without virus propagation. An immune response elicited to the S antigen protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

An ongoing, multicenter, randomized, double-blind, placebo-controlled Phase 3 Study (COV3001) (NCT04505722) is being conducted in the United States, South Africa, Brazil, Chile, Argentina, Colombia, Peru and Mexico to assess the efficacy, safety, and immunogenicity of a single-dose of the Janssen COVID-19 Vaccine for the prevention of COVID-19 in adults aged 18 years and older. Randomization was stratified by age (18-59 years, 60 years and older) and presence or absence of comorbidities associated with an increased risk of progression to severe COVID-19. The study allowed for the inclusion of individuals with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy during the 3 months preceding vaccination, as well as individuals with stable human immunodeficiency virus (HIV) infection.

A total of 44,325 individuals were randomized equally to receive Janssen COVID-19 Vaccine or saline placebo. Individuals are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The primary efficacy analysis population of 39,321 individuals (19,630 in the Janssen COVID-19 Vaccine group and 19,691 in the placebo group) included 38,059 SARSCoV-2 seronegative individuals at baseline and 1,262 individuals with an unknown serostatus. Demographic and baseline characteristics were similar among individuals who received the Janssen COVID-19 Vaccine and those who received placebo (see Table 5).

Table 5: Summary of Demographics and Baseline Characteristics - Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine (N=19,630) n (%)	Placebo (N=19,691) n (%)
Sex		
Male	10,924 (55.6)	10,910 (55.4)
Female	8,702 (44.3)	8,777 (44.6)
Age (years)		
Mean (SD)	51.1 (15.0)	51.2 (15.0)
Median	52.0	53.0
Min, max	(18; 100)	(18; 94)
Age group		
≥18 to 59 years of age	12,830 (65.4)	12,881 (65.4)
≥60 years of age	6,800 (34.6)	6,810 (34.6)
≥65 years of age	3,984 (20.3)	4,018 (20.4)
≥75 years of age	755 (3.8)	693 (3.5)
Race[a]		
White	12,200 (62.1)	12,216 (62.0)
Black or African American	3,374 (17.2)	3,390 (17.2)
Asian	720 (3.7)	663 (3.4)
American Indian/Alaska Native[b]	1,643 (8.4)	1,628 (8.3)
Native Hawaiian or other Pacific Islander	54 (0.3)	45 (0.2)
Multiple	1,036 (5.3)	1,087 (5.5)
Unknown	262 (1.3)	272 (1.4)
Not reported	341 (1.7)	390 (2.0)
Ethnicity		
Hispanic or Latino	8,793 (44.8)	8,936 (45.4)
Not Hispanic or Latino	10,344 (52.7)	10,259 (52.1)
Unknown	173 (0.9)	162 (0.8)
Not reported	319 (1.6)	333 (1.7)
Region		
Northern America (United States)	9,185 (46.8)	9,171 (46.6)
Latin America	7,967 (40.6)	8,014 (40.7)
Southern Africa (South Africa)	2,478 (12.6)	2,506 (12.7)
Comorbidities[c]		
Yes	7,830 (39.9)	7,867 (40.0)
No	11,800 (60.1)	11,824 (60.0)

[a] Some individuals could be classified in more than one category.

[b] Including 175 individuals in the United States, which represents 1% of the population recruited in the United States.

[c] Number of individuals who have 1 or more comorbidities at baseline that increase the risk of progression to severe/critical COVID-19: Obesity defined as BMI ≥30 kg/m^2 (27.5%), hypertension (10.3%), type 2 diabetes (7.2%), stable/well-controlled HIV infection (2.5%), serious heart conditions (2.4%), asthma (1.3%), and in ≤1% of individuals: cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, cystic fibrosis, immunocompromised state (weakened immune system) from blood or organ transplant, liver disease, neurologic conditions, pulmonary fibrosis, sickle cell disease, thalassemia and type 1 diabetes, regardless of age.

Efficacy Against COVID-19

The co-primary endpoints evaluated the first occurrence of moderate to severe/critical COVID-19 with onset of symptoms at least 14 days and at least 28 days after vaccination. Moderate to severe/critical COVID-19 was molecularly confirmed by a central laboratory based on a positive SARS-CoV-2 viral RNA result using a polymerase chain reaction (PCR)-based test.

- Moderate COVID-19 was defined based on the following criteria: the individual must have experienced any one of the following new or worsening signs or symptoms: respiratory rate

≥20 breaths/minute, abnormal saturation of oxygen (SpO2) but still >93% on room air at sea level, clinical or radiologic evidence of pneumonia, radiologic evidence of deep vein thrombosis (DVT), shortness of breath or difficulty breathing OR any two of the following new or worsening signs or symptoms: fever (≥38.0°C or ≥100.4°F), heart rate ≥90 beats/minute, shaking chills or rigors, sore throat, cough, malaise, headache, muscle pain (myalgia), gastrointestinal symptoms, new or changing olfactory or taste disorders, red or bruised appearing feet or toes.

- Severe/critical COVID-19 was defined based on the following criteria: the individual must have experienced any one of the following at any time during the course of observation: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation (SpO2) ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg), respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors), significant acute renal, hepatic, or neurologic dysfunction, admission to intensive care unit (ICU), death.

Final determination of severe/critical COVID-19 cases were made by an independent adjudication committee.

The median length of follow up for efficacy for individuals in the study was 8 weeks post-vaccination. Vaccine efficacy for the co-primary endpoints against moderate to severe/critical COVID-19 in individuals who were seronegative or who had an unknown serostatus at baseline was 66.9% (95% CI: 59.0; 73.4) at least 14 days after vaccination and 66.1% (95% CI: 55.0; 74.8) at least 28 days after vaccination (see Table 6).

Table 6: Analyses of Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 – With Onset at Least 14 Days and at Least 28 Days Post-Vaccination - Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine N=19,630		Placebo N=19,691		
Subgroup	COVID-19 Cases (n)	Person-Years	COVID-19 Cases (n)	Person-Years	% Vaccine Efficacy (95% CI)
14 days post-vaccination					
All subjects[a]	116	3116.6	348	3096.1	66.9 (59.0; 73.4)
18 to 59 years of age	95	2106.8	260	2095.0	63.7 (53.9; 71.6)
60 years and older	21	1009.8	88	1001.2	76.3 (61.6; 86.0)
28 days post-vaccination					
All subjects[a]	66	3102.0	193	3070.7	66.1 (55.0; 74.8)[b]
18 to 59 years of age	52	2097.6	152	2077.0	66.1 (53.3; 75.8)
60 years and older	14	1004.4	41	993.6	66.2 (36.7; 83.0)

[a] Co-primary endpoint.
[b] The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.

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Vaccine efficacy against severe/critical COVID-19 at least 14 days after vaccination was 76.7% (95% CI: 54.6; 89.1) and 85.4% (95% CI: 54.2; 96.9) at least 28 days after vaccination (see Table 7).

Table 7: Analyses of Vaccine Efficacy: Secondary Endpoints of Centrally Confirmed Severe/Critical COVID-19 – in Adults 18 Years of Age and Older With Onset at Least 14 Days and at Least 28 Days Post-Vaccination – Primary Efficacy Analysis Population

	Janssen COVID-19 Vaccine N=19,630		Placebo N=19,691		
Subgroup	**COVID-19 Cases (n)**	**Person-Years**	**COVID-19 Cases (n)**	**Person-Years**	**% Vaccine Efficacy (95% CI)**
14 days post-vaccination					
Severe/critical	14	3125.1	60	3122.0	76.7 (54.6; 89.1)[a]
28 days post-vaccination					
Severe/critical	5	3106.2	34	3082.6	85.4 (54.2; 96.9)[a]

[a] The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions.

Among all COVID-19 cases with onset at least 14 days post vaccination, including cases diagnosed by a positive PCR from a local laboratory and still awaiting confirmation at the central laboratory, there were 2 COVID-19 related hospitalizations in the vaccine group (with none after 28 days) and 29 in the placebo group (with 16 after 28 days).

As of the primary analysis cut-off date of January 22, 2021, there were no COVID-19-related deaths reported in Janssen COVID-19 Vaccine recipients compared to 5 COVID-19-related deaths reported in placebo recipients, who were SARS-CoV-2 PCR negative at baseline.

Janssen COVID-19 Vaccine Efficacy in Countries With Different Circulating SARS-CoV-2 Variants.

Exploratory subgroup analyses of vaccine efficacy against moderate to severe/critical COVID-19 and severe/critical COVID-19 for Brazil, South Africa, and the United States were conducted (see Table 8). For the subgroup analyses, all COVID-19 cases accrued up to the primary efficacy analysis data cutoff date, including cases confirmed by the central laboratory and cases with documented positive SARS-CoV-2 PCR from a local laboratory which are still awaiting confirmation by the central laboratory, were included. The concordance rate observed up to the data cut-off date between the PCR results from the local laboratory and the central laboratory was 90.3%.

Table 8: Summary of Vaccine Efficacy against Moderate to Severe/Critical and Severe/Critical COVID-19 for Countries With >100 Reported Moderate to Severe/Critical Cases

		Severity	
	Onset	Moderate to Severe/Critical Point estimate (95% CI)	Severe/Critical Point estimate (95% CI)
US	at least **14 days** after vaccination	74.4% (65.0; 81.6)	78.0% (33.1; 94.6)
	at least **28 days** after vaccination	72.0% (58.2;81.7)	85.9% (-9.4; 99.7)
Brazil	at least **14 days** after vaccination	66.2% (51.0; 77.1)	81.9% (17.0; 98.1)
	at least **28 days** after vaccination	68.1% (48.8; 80.7)	87.6% (7.8; 99.7)
South Africa	at least **14 days** after vaccination	52.0% (30.3; 67.4)	73.1% (40.0; 89.4)
	at least **28 days** after vaccination	64.0% (41.2; 78.7)	81.7% (46.2; 95.4)

Strain sequencing was conducted on available samples with sufficient viral load from centrally confirmed COVID-19 cases (one sequence per case). As of February 12, 2021, samples from 71.7% of central laboratory confirmed primary analysis cases had been sequenced [United States (73.5%), South Africa (66.9%) and Brazil (69.3%)]. In the United States, 96.4% of strains were identified as the Wuhan-H1 variant D614G; in South Africa, 94.5% of strains were identified as the 20H/501Y.V2 variant (B.1.351 lineage); in Brazil, 69.4% of strains were identified to be a variant of the P.2 lineage and 30.6% of strains were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, SARS-CoV-2 variants from the B1.1.7 or P.1 lineages were not found in any of the sequenced samples.

19 HOW SUPPLIED/STORAGE AND HANDLING

Janssen COVID-19 Vaccine is supplied in a carton of 10 multi-dose vials (NDC 59676-580-15). A maximum of 5 doses can be withdrawn from the multi-dose vial.

The storage and handling information in this Fact Sheet supersedes the storage and handling information on the carton and vial labels.

Storage Prior to First Puncture of the Vaccine Vial

Store unpunctured multi-dose vials of the Janssen COVID-19 Vaccine at 2°C to 8°C (36°F to 46°F) and protect from light. Do not store frozen.

Unpunctured vials of Janssen COVID-19 Vaccine may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours.

The Janssen COVID-19 Vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately, thaw at room temperature (maximally 25°C/77°F). At room temperature (maximally 25°C/77°F), a carton of 10 vials will take approximately 2 hours to thaw, and an individual vial will take approximately 1 hour to thaw. Do not refreeze once thawed.

Storage After First Puncture of the Vaccine Vial

After the first dose has been withdrawn, hold the vial between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. Discard the vial if vaccine is not used within these times.

Revised: Apr/23/2021

20 PATIENT COUNSELING INFORMATION

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

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

21 CONTACT INFORMATION

For general questions or to access the most recent Janssen COVID-19 Vaccine Fact Sheets, scan the QR code using your device, visit www.janssencovid19vaccine.com or call the telephone numbers provided below.

QR Code	Fact Sheets Website	Telephone numbers
	www.janssencovid19vaccine.com.	US Toll Free: 1-800-565-4008 US Toll: 1-908-455-9922

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.janssencovid19vaccine.com.

Manufactured by:
Janssen Biotech, Inc.
a Janssen Pharmaceutical Company of Johnson & Johnson
Horsham, PA 19044, USA

Revised: Apr/23/2021

Exhibit 12

Janssen: Letter of Authorization from Denise M. Hinton, Chief Scientist, FDA, to Janssen Biotech, Inc. (June 10, 2021)

U.S. FOOD & DRUG ADMINISTRATION

June 10, 2021

Janssen Biotech, Inc.
Attention: Ms. Ruta Walawalkar
920 Route 202
Raritan, NJ 08869

Dear Ms. Walawalkar:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food Drug and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to terms of any authorization issued under that section.[2]

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of the Janssen COVID-19 Vaccine for the prevention of COVID-19 for individuals 18 years of age and older pursuant to Section 564 of the Act.

On June 10, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 27, 2021 letter in its entirety with revisions incorporated to clarify terms and conditions that relate to export of Janssen COVID-19 Vaccine from the United States.

The Janssen COVID-19 Vaccine is for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. The vaccine contains a recombinant, replication-incompetent human adenovirus serotype 26 (Ad26) vector, encoding the SARS-CoV-2 viral spike (S) glycoprotein, stabilized in its pre-fusion form. It is an investigational vaccine not licensed for any indication.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

FDA reviewed safety and efficacy data from an ongoing phase 3 trial which has enrolled 43,783 participants randomized 1:1 to receive Janssen COVID-19 Vaccine or saline control. The trial has enrolled participants 18 years of age and older. FDA's review has considered the safety and effectiveness data as they relate to the request for emergency use authorization. FDA's review of the available safety data from 43,783 participants 18 years of age and older, who were followed for a median duration of eight weeks after receiving the vaccine or placebo, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the efficacy data from 39,321 participants 18 years of age and older who were SARS-CoV-2 seronegative or who had an unknown serostatus at baseline show that the vaccine was 66.9% effective (95% confidence interval (CI): 59.0, 73.4) and 66.1% effective (95% CI: 55.0, 74.8) in preventing moderate to severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination, respectively. Based on these data, and review of manufacturing information regarding product quality and consistency, it is reasonable to believe that the Janssen COVID-19 Vaccine may be effective. Additionally, it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of the Janssen COVID-19 Vaccine outweigh its known and potential risks, for the prevention of COVID-19 in individuals 18 years of age and older. Finally, on February 26, 2021, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of the Janssen COVID-19 Vaccine for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the Janssen COVID-19 Vaccine for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the Janssen COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of the Janssen COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

3. There is no adequate, approved, and available alternative to the emergency use of the Janssen COVID-19 Vaccine to prevent COVID-19.[3]

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Janssen Biotech, Inc. will supply the Janssen COVID-19 Vaccine, either directly or through authorized distributor(s)[4] to emergency response stakeholders[5] as directed by the U.S. government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA;
- The Janssen COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[6] and used only to prevent COVID-19 in individuals ages 18 and older; and
- The Janssen COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

Product Description

The Janssen COVID-19 Vaccine is supplied as a suspension in multi-dose vials. The Janssen COVID-19 Vaccine does not contain a preservative.

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[4] "Authorized Distributor(s)" are identified by Janssen Biotech, Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Janssen COVID-19 Vaccine.

[5] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

[6] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

Each 0.5 mL dose of the Janssen COVID-19 Vaccine is formulated to contain $5x10^{10}$ virus particles of the Ad26 vector encoding the S glycoprotein of SARS-CoV-2. Each dose of the Janssen COVID-19 Vaccine also includes the following inactive ingredients 2.19 mg sodium chloride, 0.14 mg citric acid monohydrate, 2.02 mg trisodium citrate dihydrate, 0.16 mg polysorbate-80, 25.5 mg 2-hydroxypropyl-B-cyclodextrin, 2.04 mg ethanol. Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng).

The dosing regimen is a single dose of 0.5 mL

The manufacture of the authorized Janssen COVID-19 Vaccine is limited to those facilities identified and agreed upon in Janssen's request for authorization.

The Janssen COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Janssen COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

The Janssen COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of the Janssen COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19)

- Fact Sheet for Recipients and Caregivers: Emergency Use Authorization (EUA) of the Janssen COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) in Individuals 18 Years of Age and Older

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the Janssen COVID-19 Vaccine, when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the Janssen COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that the Janssen COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the Janssen COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), the Janssen COVID-19 Vaccine is authorized to prevent COVID-19 in individuals 18 years of age and older as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Janssen Biotech, Inc. and Authorized Distributor(s)

A. Janssen Biotech, Inc. and authorized distributor(s) will ensure that the authorized Janssen COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Janssen Biotech, Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Janssen Biotech, Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving the authorized Janssen COVID-19 Vaccine. Janssen Biotech, Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Janssen Biotech, Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Janssen Biotech, Inc. may request changes to this authorization, including to the authorized Fact Sheets for the Janssen COVID-19 Vaccine. Any request for changes to this EUA must be submitted to the Office of Vaccines Research and Review

(OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[7]

F. Janssen Biotech, Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Janssen Biotech, Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Janssen Biotech, Inc.

G. Janssen Biotech, Inc. must submit to Investigational New Drug application (IND) number 22657 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER, beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest.
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
- Newly identified safety concerns in the interval; and
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by the Agency.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Janssen Biotech, Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

[7] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. All changes to the authorization require review and concurrence from OVRR. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is also required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

K. Janssen Biotech, Inc. will submit to the EUA file quarterly manufacturing reports that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report. The first report is due June 1, 2021.

L. Janssen Biotech, Inc. and authorized distributor(s) will maintain records regarding release of Janssen COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Janssen Biotech, Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Janssen Biotech, Inc. will conduct post-authorization observational studies to evaluate the association between Janssen COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Janssen COVID-19 Vaccine under this EUA in the general U.S. population (18 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Janssen Biotech, Inc. will provide protocols and status update reports to the IND 22657 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Janssen COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Janssen COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Fact Sheet for Recipients and Caregivers to each individual receiving vaccination.

T. Vaccination providers administering the Janssen COVID-19 Vaccine must report the following information associated with the administration of the Janssen COVID-19 Vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of Multisystem Inflammatory Syndrome in adults
   - Cases of COVID-19 that result in hospitalization or death

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Janssen COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Janssen Biotech, Inc. by contacting 1-800-565-4008 or by providing a copy of the VAERS form to Janssen Biotech, Inc.; Fax: 215-293-9955, or by email JNJvaccineAE@its.jnj.com.

U. Vaccination providers will conduct any follow-up requested by the U.S. government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Janssen COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Janssen COVID-19 Vaccine clearly and conspicuously shall state that:
   - This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 18 years of age and older; and
   - The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the product is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Exhibit 13

Janssen: COVID-19 Vaccine Emergency Use Authorization Review Memorandum (Feb. 27, 2021)

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	27205
Sponsor	Janssen Biotech, Inc.
Submission Date	February 4, 2021
Receipt Date	February 4, 2021
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Principal Discipline Reviewers from the Review Team	Sudhakar Agnihothram, Ph.D., Committee chair, OVRR/DVRPA; Bharat Khurana, DVM, Ph.D., MBA, Regulatory Project Manager, OVRR/DVRPA; Rachel Zhang, M.D., Clinical reviewer, OVRR/DVRPA; Yosefa Hefter, M.D., Clinical reviewer, OVRR/DVRPA; Claudia Wrzesinski, Ph.D., Toxicology reviewer, OVRR/DVRPA; Ye Yang, Ph.D., Biostatistics reviewer, OBE/DB; Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Marian Major, Ph.D., CMC/Product reviewer, OVRR/DVP; Alla Kachko, Ph.D., CMC/Product reviewer, OVRR/DVP; Pankaj (Pete) Amin, B.S., CMC/Facility reviewer; OCBQ/DMPQ; Holly Brevig, Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Jane Woo, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Haecin Chun, M.S., BIMO reviewer, OCBQ/DIS/BMB; Bhanu Kannan, M.S., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Pharm.D., MPH, Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	February 27, 2021
Established Name/Other names used during development	Janssen COVID-19 vaccine (Ad26.COV2.S)
Dosage Forms/Strengths and Route of Administration	A 0.5 mL suspension administered as a single intramuscular injection at the dose level of 5×10^{10} virus particles (vp)
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 18 years of age and older

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Glossary

Ad26	adenovirus type 26
AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
BIMO	Bioresearch Monitoring
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	chemistry, manufacturing and control
COVID-19	coronavirus disease 2019
CT	computed tomography
DP	drug product
DS	drug substance
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
LMP	last menstrual period
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical Resource Utilization
PT	preferred term
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standard MedDRA query
SAP	statistical analysis plan
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
vp	virus particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic presents an extraordinary challenge to global health and, as of February 26, 2021, has caused more than 113 million cases of COVID-19 and claimed the lives of more than 2.5 million people worldwide. In the United States, more than 28 million cases and 503,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an Emergency Use Authorization (EUA) for a COVID-19 vaccine after determining that certain statutory requirements are met.

On February 4, 2021, Janssen Biotech, Inc. (the Sponsor, also referred to as Janssen) submitted an EUA request to FDA for an investigational vaccine intended to prevent COVID-19 caused by SARS-CoV-2. The Janssen COVID-19 vaccine, also referred to as Ad26.COV2.S, is a replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein. The proposed use under an EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is a single intramuscular injection at the dose level of 5×10^{10} virus particles (vp).

The EUA request includes safety and efficacy data from an ongoing multi-national Phase 3 randomized, double-blind and placebo-controlled trial of a single dose ($5x10^{10}$ vp) of Ad26.COV2.S in approximately 40,000 participants. The protocol-specified primary analysis evaluated co-primary efficacy endpoints of molecularly confirmed, moderate to severe/critical COVID-19 with onset at least 14 and 28 days, respectively, after vaccination in participants without evidence of SARS-CoV-2 infection prior to vaccination. The co-primary efficacy analysis (data cutoff of January 22, 2021) included 39,321 randomized (1:1) participants with a median follow-up time of 2 months post-vaccination.

Vaccine efficacy (VE) against central laboratory-confirmed moderate to severe/critical COVID-19 across all geographic areas in which the trial was conducted was 66.9% (95% CI 59.0, 73.4) when considering cases occurring at least 14 days after the single-dose vaccination and 66.1% (55.0, 74.8) when considering cases occurring at least 28 days after vaccination. For the vaccine and placebo groups, respectively, there were 116 and 348 COVID-19 cases that occurred at least 14 days after vaccination, and 66 and 193 cases that occurred at least 28 days after vaccination. Analyses of secondary endpoints demonstrated vaccine efficacy against central laboratory confirmed and blind-adjudicated severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination of 76.7% (54.6, 89.1) and 85.4% (54.2, 96.9), respectively. VE estimates for prevention of moderate to severe/critical COVID-19 and for prevention of severe/critical COVID-19 including positive PCR results still awaiting confirmation by the central laboratory were similar (but with narrower confidence intervals) to the VE estimates that included only centrally confirmed cases. In a post hoc analysis of all COVID-19 related hospitalizations starting 14 days after vaccination, including non-centrally confirmed cases, there were 2 cases in the vaccine group (with no cases after 28 days) compared with 29 cases in the placebo group (with 16 cases after 28 days). As of February 5, 2021, there were 7 COVID-19 related deaths in the study in the placebo group and no COVID-19 related deaths in the vaccine group.

In general, VE among the subgroups (age, comorbidity, race, ethnicity) appears to be similar to the VE in the overall study population. A lower VE estimate was observed for the subgroup of

participants 60 years of age and older with comorbidities compared with the overall population, but with an observed trend of increasing VE with narrower confidence intervals as numbers of cases included in the analysis increased (i.e., counting cases from 14 days rather than 28 days and including cases not yet centrally confirmed). There were no COVID-19-related deaths and no COVID-19 cases requiring medical intervention occurring 28 days or more post-vaccination among participants age 60 years or older with medical comorbidities in the vaccine group. The VE results for some other subgroups with small numbers of participants (≥75 years of age, certain racial subgroups) have limited interpretability. Data were insufficient to assess VE in participants with evidence of prior SARS-CoV-2 infection.

There was country-to-country variation in VE estimates for the prevention of moderate to severe/critical COVID-19 and severe/critical COVID-19, but the confidence intervals were overlapping. Predominant strains among those sequenced were Wuhan-H1 variant D614G in the U.S. (96.4% of sequenced cases), 20H/501Y.V2 variant (B.1.351) in South Africa (94.5% of sequenced cases), and variant of the P.2 lineage in Brazil (69.4% of sequenced cases, with the remaining 30.6% Wuhan-H1 variant D614G). There were no cases identified as B.1.1.7 or P1 lineages as of February 12, 2021.

Safety analysis through the January 22, 2021 data cutoff included 43,783 randomized (1:1) participants ≥18 years of age with 2-month median follow-up. The analysis supported a favorable safety profile with no specific safety concerns identified that would preclude issuance of an EUA.

A subset of participants (N=6,736) was followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. The most common solicited adverse reactions associated with Ad26.COV2.S were injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and myalgia (33.2%); these were predominately mild and moderate, with 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, reported as grade 3. Reports of solicited reactions were less common among participants ≥60 years of age. Reactogenicity to Ad26.COV2.S in adults ≥18 years of age was demonstrated to be transient, and most solicited adverse events (AEs) generally resolved in 1 to 2 days post-vaccination. There were no meaningful imbalances between vaccine and placebo recipients in unsolicited adverse events reported during the 28 days following vaccination.

Among all adverse events collected through the January 22, 2021 data cutoff, a numerical imbalance was seen in non-serious urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days following vaccination which is possibly related to the vaccine. Numerical imbalances were observed between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0). Data at this time are insufficient to determine a causal relationship between these events and the vaccine. There were no other notable patterns or numerical imbalances in the available data as of the cutoff date between treatment groups for specific categories of adverse events that would suggest a causal relationship to Ad26.COV2.S.

Non-fatal serious adverse events, excluding those attributed to COVID-19, were infrequent and balanced between study groups with respect to rates and types of events (0.4% in both groups). One serious event of a hypersensitivity reaction, not classified as anaphylaxis, beginning two days following vaccination was likely related to receipt of the vaccine. During FDA review of the EUA request, the Sponsor reported a case of anaphylaxis following vaccination with Ad26.COV2.S, the details of which are still under investigation, in an ongoing, open-label study in South Africa.

There was more frequent, generally mild to moderate reactogenicity in participants 18 to 59 years of age compared to older participants. There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Occurrence of solicited, unsolicited, and serious adverse events in these subgroups was generally consistent with the overall study population.

Non-clinical toxicology studies with Ad26.COV2.S including a combined developmental and perinatal/postnatal reproductive toxicity study did not raise specific safety concerns, and other non-clinical studies support the vaccine's immunogenicity, reduction of SARS-CoV-2 pulmonary and nasal viral load in animal challenge models, and absence of findings suggesting risk of vaccine-enhanced disease.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021, originally issued October 2020).[1] FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on February 26, 2021. Following a discussion of the data presented, the VRBPAC voted 22-0 in favor of a determination that based on the totality of scientific evidence available, the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older. Following review of information submitted in support of the EUA request and considering the VRBPAC's recommendations, the review team concludes that:

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Janssen COVID-19 vaccine may be effective to prevent such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.
- There is no adequate, approved, and available alternative to the product for preventing COVID-19 caused by SARS-CoV-2.

The review team therefore recommends issuance of an EUA for use of the Janssen COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of February 26, 2021, has caused more than 113 million cases of COVID-19 and claimed the lives of more than 2.5 million people worldwide. In the United States, more than 28 million cases and

503,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[2] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[3] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome.[4] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[5] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. FDA issued emergency use authorizations for two mRNA vaccines, developed by Pfizer and Moderna, respectively, in December 2020. Other COVID-19 vaccines currently in development are based on various platforms and include mRNA, DNA, viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 Available Vaccines and Therapies for COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under EUA, but not FDA approved, for treatment of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older, administered as 2 doses 3 weeks apart. On December 18, 2020, FDA issued an EUA for the Moderna COVID-19 vaccine for use in individuals 18 years of age and older, administered as 2 doses 4 weeks apart. These COVID-19 vaccines are considered unapproved products, and current supplies are insufficient to vaccinate all persons in the U.S. for whom use of the vaccines are authorized. Thus, there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

2.3 EUA Request for the Janssen COVID-19 Vaccine

Janssen Biotech, Inc. is developing a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein, to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Janssen's Ad26.COV2.S vaccine is administered as a single intramuscular injection of $5x10^{10}$ vp. The vaccine is supplied

as a multidose vial (5 doses) containing a refrigerated suspension with a shelf life of 3 months when stored at 2º to 8º C. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial of the single-dose Ad26.COV2.S in approximately 40,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. The primary analysis of 39,321 participants using a data cutoff date of January 22, 2021 demonstrated vaccine efficacy (VE) of 66.9% (adjusted 95% CI 59.0%, 73.4%) for the prevention of moderate to severe/critical COVID-19 occurring at least 14 days vaccination, and 66.1% (adjusted 95% CI 55.0%, 74.8%) for the prevention of cases occurring at least 28 days after vaccination. Safety data from a January 22, 2021 data cutoff with a median of 58 days follow-up after vaccination were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On February 4, 2021, Janssen Biotech, Inc. submitted an EUA request to FDA, based on the primary analyses described above, for Ad26.COV2.S for active immunization for the prevention of COVID-19 in adults 18 years of age and older.

2.4 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[6]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product

tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.5 Applicable Guidance for Industry

An EUA for a COVID-19 vaccine allows for the rapid and widespread deployment for administration to millions of individuals, including healthy people and thus, data are needed demonstrating that the known and potential benefits of the vaccine outweigh its known and potential risks. FDA published guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021, originally issued October 2020) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[7]

Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. Data adequate to inform an assessment of the vaccine's benefits and risks, and thus support issuance of an EUA, would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry Development and Licensure of Vaccines to Prevent COVID-19 (June 2020) (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] From the perspective of

vaccine efficacy, a 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle requests for unblinding and crossover of placebo recipients to receive vaccine in the trial and loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

3. Janssen COVID-19 Vaccine

3.1 Vaccine Composition, Dosing Regimen

The Janssen COVID-19 vaccine is a colorless to slightly yellow, clear to very opalescent sterile suspension for intramuscular injection. The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the SARS-CoV-2 spike (S) protein in a stabilized conformation. The vaccine also contains the following inactive ingredients: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate 80, sodium chloride.

The Ad26 vector expressing the SARS-CoV-2 S protein is grown in PER.C6 TetR cells in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients and filled into vials. Each 0.5 mL dose of Janssen COVID-19 vaccine is formulated to contain 5×10^{10} virus particles. The Janssen COVID-19 vaccine is administered intramuscularly as a single-dose (0.5 mL). The vaccine is provided as a refrigerated suspension [stored at 2°C to 8°C (36°F to 46°F)] in a multi-dose vial containing 5 doses (0.5 mL each). The vials should be protected from light. Unpunctured vials may be stored between 9°C to 25°C (47°F to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. The vial should be discarded if the vaccine is not used within these times.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's guidance Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021, originally issued October 2020). As such, FDA has determined that the Sponsor has provided adequate

information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

3.2 Safety Experience of Ad26-based Vaccines

The Janssen COVID-19 vaccine is based on the Ad26 vector platform. Clinical experience with the Ad26 platform consists of the Ad26.ZEBOV/MVA-BN-Filo Ebola vaccine regimen (approved by the European Medicines Agency on July 1, 2020) and investigational vaccines against Zika, filovirus, HIV, HPV, malaria, and respiratory syncytial virus. As of 31 December 2020, Ad26-based vaccines have been used to vaccinate 193,831 participants in clinical studies and vaccination programs. Overall, these vaccines have been shown to have an acceptable clinical safety profile to date.

3.3 Proposed Use Under EUA

The proposed use of the Ad26.COV2.S vaccine under an EUA is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

4. FDA Review of Clinical Safety and Effectiveness Data

4.1 Overview of Clinical Studies

There are five ongoing clinical studies with Ad26.COV2.S, which are summarized in Table 1 below. All listed trials are randomized, double-blind, and placebo-controlled. Study VAC31518COV3001 (Study 3001) is a Phase 3 efficacy and safety study with a single-dose regimen and is the focus of the EUA review. Study 3009 is a Phase 3 efficacy and safety study with a 2-dose regimen than began in November 2020, for which only blinded safety data was available at the time of the EUA request. Study 2001 is a Phase 2a dose-ranging study exploring 4 dose levels and 1-dose and 2-dose regimens in adults and adolescents and will not be discussed in detail. Studies 1002 and 1001 are Phase 1 dose-ranging studies and will also not be discussed in detail. Summaries of the designs and results to date of Studies 1001, 1002, 2001, and 3009 may be found in Appendix A, page 67.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Janssen COVID-19 Vaccine

Study Number	Phase Type (Efficacy, Safety)	Participants Planned (N)	Test Product(s); Dosing Regimens	Study Status
3001	Phase 3 efficacy, safety	40,000 adults	Ad26.COV2.S $5x10^{10}$ vp 1-dose regimen	Enrollment complete
3009	Phase 3, efficacy, safety	30,000 adults	Ad26.COV2.S $5×10^{10}$ vp 2-dose regimen	Enrollment ongoing
2001	Phase 2a safety, immunogenicity	550 adults 660 adolescents	Ad26.COV2.S $1×10^{11}$ vp $5×10^{10}$ vp $2.5x10^{10}$ vp $1.25x10^{10}$ vp; 1-dose and 2-dose regimens	Enrollment of adults ongoing; enrollment of adolescents not started

Study Number	Phase Type (Efficacy, Safety)	Participants Planned (N)	Test Product(s); Dosing Regimens	Study Status
1002	Phase 1 safety, immunogenicity	250 adults	Ad26.COV2.S 5×10^{10} vp, 1×10^{11} vp; 2-dose regimen	Enrollment complete
1001	Phase 1/2a safety, immunogenicity	1045 adults	Ad26.COV2.S 5×10^{10} vp and 1×10^{11} vp; 1-dose and 2-dose regimens, with booster in 1 cohort	Enrollment complete

4.2 Study 3001

4.2.1 Design

Study 3001 is an ongoing randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of Ad26.COV2.S administered as a single dose in adults ≥18 years of age. A target of 40,000 adults were to be randomized 1:1 to receive intramuscular injections of either vaccine ($5x10^{10}$ vp) or saline placebo. At least 30% of the total study population was to consist of participants ≥60 years of age, and enrollment of participants 18 to 40 years of age was limited to approximately 20% of the total study population.

A staged enrollment strategy was specified in the protocol. Following acceptable safety and immunogenicity data from Study 1001 to support the dosing regimen, Study 3001 enrolled approximately 2000 participants 18 to 59 years of age without comorbidities (stage 1a). As no safety issues were identified during the Data Safety Monitoring Board's examination of safety data through Day 3 post-vaccination, participants 18 to 59 years with and without co-morbidities were enrolled (stage 1b). In parallel, approximately 2000 participants ≥60 years of age without comorbidities were enrolled (stage 2a) followed by a pause in vaccination for evaluation safety data through Day 3 post-vaccination prior to enrollment of ≥60-year-olds with and without comorbidities (stage 2b).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. For the initial diagnosis of SARS-CoV-2 infection, FDA-authorized PCR tests were used, irrespective whether the test was performed locally at study sites or at the central laboratory (University of Washington [UW Virology laboratory]). Samples from locally diagnosed COVID-19 cases were to be sent to the central laboratory for confirmatory testing. Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay) by the central laboratory was required to meet the co-primary and secondary efficacy endpoint case definitions.

The co-primary endpoints were efficacy of a single dose of vaccine to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring (1) at least 14 days after vaccination and (2) at least 28 days after vaccination in study participants without evidence of prior SARS-CoV-2 infection at baseline. Evaluation of the co-primary endpoints was triggered by prespecified criteria:

1. The first 50% of participants have at least 2 months of follow-up after vaccination

2. At least 42 moderate to severe/critical cases of COVID-19 with onset at least 28 days after vaccination
3. At least 6 cases of COVID-19 among participants ≥60 years of age (onset ≥28 days after vaccination)
4. At least 5 severe/critical cases of COVID-19 in the placebo group (onset ≥28 days after vaccination) with a favorable vaccine-to-placebo split for both co-primary endpoints.

The protocol-specified "final analysis" will be performed when the last participant completes the visit 12 months post-vaccination or discontinues earlier. The end-of-study analysis will be performed when all participants have completed the visit 24 months post-vaccination or discontinued earlier. The expected duration of study participation is approximately 25 months.

Case Definitions

The case definition for moderate COVID-19 was a SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal, throat, sputum, saliva) or other sample, **and** at any time during the course of observation:

Any 1 of the following new or worsening signs or symptoms:

- Respiratory rate ≥20 breaths/minute
- Abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level
- Clinical or radiologic evidence of pneumonia
- Radiologic evidence of deep vein thrombosis
- Shortness of breath or difficulty breathing

OR

Any 2 of the following new or worsening signs or symptoms:

- Fever (≥38.0°C or ≥100.4°F)
- Heart rate ≥90 beats/minute
- Shaking chills or rigors
- Sore throat
- Cough
- Malaise as evidenced by loss of appetite, fatigue, physical weakness, and/or feeling unwell
- Headache
- Muscle pain (myalgia)
- Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)
- New or changing olfactory or taste disorders
- Red or bruised looking feet or toes

The case definition for severe/critical COVID-19 was a RT-PCR or molecular test result from samples described above **and** any one of the following at any time during the course of observation:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths/minute, heart rate ≥125 beats/minute, oxygen saturation [SpO_2] ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2] <300 mmHg)
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to the ICU
- Death

All cases meeting the severe/critical criteria were adjudicated by a blinded clinical severity adjudication committee to determine if the case was severe/critical in their judgement. Additionally, all cases meeting the moderate case definition and that included >3 signs and/or symptoms from the list of signs and symptoms were evaluated by the clinical severity adjudication committee to determine if the case was severe/critical in their judgement.

Primary Efficacy Endpoint

The originally specified primary endpoint was efficacy of the vaccine to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring at least 14 days post-vaccination in SARS-CoV-2 seronegative adults (with "seronegative" defined as negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). Study protocol amendment 3 (December 14, 2020) added a co-primary endpoint counting COVID-19 cases from 28 days post-vaccination.

The primary analysis was based on the per-protocol set defined as those participants in the full analysis set (FAS) who received study vaccine, were seronegative at the time of vaccination, and had no major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

A successful primary efficacy conclusion required two conditions:

1. Rejecting the null hypothesis H_0: VE ≤30% for each co-primary endpoint at a 2.5% one-sided significance level and a VE point estimate ≥50% for each co-primary endpoint;

   and

2. A favorable split vaccine:placebo for the subset of primary endpoints meeting the severe/critical COVID-19 case definition (expressed as a VE point estimate against severe/critical COVID-19 molecularly confirmed endpoints ≥50%) and a minimum of 5 events in the placebo group. This requirement needed to be met for severe/critical events with onset at least 14 days after vaccination and 28 days after vaccination.

Both conditions 1 and 2 simultaneously had to be met for both co-primary endpoints at the same calendar timepoint. Exact Poisson regression was used to estimate VE and associated confidence intervals taking into account the follow-up time.

Secondary Efficacy Endpoints

Secondary endpoints included vaccine efficacy to prevent or vaccine impact on:

- Severe/critical COVID-19
- COVID-19 requiring medical intervention
- COVID-19-related death
- Any symptomatic COVID-19
- Asymptomatic COVID-19 as inferred through seroconversion
- COVID-19 per the FDA harmonized COVID-19 case definition

Vaccine efficacy of selected secondary endpoints was evaluated against a null hypothesis employing a lower limit VE >0% once hypothesis testing met the respective success criteria and data requirements for both co-primary endpoints. The case definition for mild COVID-19 (included in any symptomatic disease) and the FDA harmonized COVID-19 case definition may be found in Appendix B, page 69.

Evaluation of Safety

In Study 3001, the safety objective was evaluation of the safety of Ad26.COV2.S following vaccination. In a subset of participants (n=6736), local and systemic reactions were recorded from for 7 days following vaccination, and unsolicited AEs were collected from vaccination to day 28 after vaccination. In all participants, medically attended adverse events (MAAEs) were collected from vaccination to 6 months after vaccination, and MAAEs leading to study discontinuation and serious AEs (SAEs) were collected from vaccination to the end of the study.

Safety assessments included the following:

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following vaccination. Solicited ARs were recorded daily using eDiaries
- Unsolicited AEs observed or reported during the 28 days following vaccination. Unsolicited AEs are those not included in the protocol-defined solicited ARs
- Medically attended adverse events (MAAEs) from Day 1 through 6 months after vaccination
- MAAEs leading to discontinuation from study participation from Day 1 through 104 weeks following vaccinations
- SAEs from Day 1 through 104 weeks following vaccination or withdrawal from the study
- Vital sign measurements
- Physical examination findings
- Pregnancy and accompanying outcomes

AEs, including SAEs, associated with molecularly confirmed SARS-CoV-2 infection were removed from the analysis of adverse events.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. A stopping rule would be triggered if the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Table 2. Analysis Populations

Population	Description
Randomized	All participants who are randomized, regardless of the treatment status during the study.
Full analysis set	All randomized participants with a documented study vaccine administration. The FAS was used for all analyses of safety except solicited adverse reactions.
Per-protocol set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 at the time of vaccination and no major protocol deviations that were judged to possibly impact the efficacy of the vaccine.
Safety subset	Subset of the full analysis set for the analysis of solicited and unsolicited AEs.

4.2.2 Compliance with Good Clinical Practice

As summarized in Section 5.6 (Inspections of Clinical Study Sites), Bioresearch Monitoring (BIMO) inspections were conducted at five domestic clinical investigator sites participating in the conduct of the trial.

4.2.3 FDA Assessment of Phase 3 Follow-Up Duration

At the time of the primary analysis, the median follow-up duration for participants in the efficacy and safety analysis populations was 8 weeks after vaccination, which FDA considers to be equivalent to 2 months and which meets the FDA expectation for follow-up after completion of the full vaccination regimen. Phased enrollment by age group and comorbidity risk resulted in slight differences in follow-up time between participants in these groups, with an approximately 2-week difference in the median follow up time between the first group enrolled (18-59 without comorbidities) and last group enrolled (60 years and older with comorbidities). Table 3 shows the median follow-up time by age and comorbidities in the FAS. Follow-up time in the per-protocol set is similar (data not shown).

Table 3. Participant Disposition by Age Group and Comorbidities, Full Analysis Set, Study 3001

Participant Group Follow-up	Ad26.COV2.S N=21895	Placebo N=21888	All Participants N=43783
18-59 overall	14564	14547	29111
Participants with at least 8 weeks follow-up	62.8%	63.1%	63.0%
Median follow-up after vaccination in days	61.0	61.0	61.0
18-59, no comorbidities	9332	9371	18703
Participants with at least 8 weeks follow-up	70.0%	69.9%	70.0%
Median follow-up after vaccination in days	64.0	64.0	64.0
18-59, with comorbidities	5232	5176	10408
Participants with at least 8 weeks follow-up	49.9%	50.8%	50.4%
Median follow-up after vaccination in days	56.0	57.0	57.0
≥60 years overall	7331	7341	14672
Participants with at least 8 weeks follow-up	38.2%	37.8%	38.0%
Median follow-up after vaccination in days	52.0	52.0	52.0
≥60 years, no comorbidities	3627	3595	7222
Participants with at least 8 weeks follow-up	47.6%	49.0%	48.3%
Median follow-up after vaccination in days	54.0	55.0	54.0

Participant Group Follow-up	Ad26.COV2.S N=21895	Placebo N=21888	All Participants N=43783
≥60 years, with comorbidities	3704	3746	7450
Participants with at least 8 weeks follow-up	29.0%	27.1%	28.0%
Median follow-up after vaccination in days	50.0	50.0	50.0

Source:Sponsor table TSIDS08

4.2.4 Participant Disposition and Inclusion in Analysis Populations

The tables below show the disposition of participants in the efficacy analysis population (Table 4) and safety analysis population (Table 5). The proportions of participants excluded from the per-protocol set were balanced between treatment groups, with the majority of those excluded due to positive baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per-protocol set, 54.6% of vaccine recipients and 54.7% of placebo recipients completed at least 8 weeks follow-up after vaccination. As of the data cutoff date, 5.3% of participants in the vaccine group and 5.8% of participants in the placebo group in the per-protocol set were unblinded by request after they became eligible to receive an authorized COVID-19 vaccine under EUA. A slightly greater proportion of participants ≥60 years of age were unblinded (6.6%) compared to those 18 to 59 years of age (4.4%). The vast majority (93.0%) of participants who were unblinded were from US study sites. These participants were included in the per-protocol set until the time of the unblinding.

Table 4. Disposition[a], Efficacy Analysis Population, Study 3001

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Randomized	22174	22151	44325
Vaccinated[a]	21895	21888	43783
Full analysis set	21895 (100.0)	21888 (100.0)	43783 (100.0)
Participants excluded from per-protocol set	2265 (10.3)	2197 (10.0)	4462 (10.2)
Positive SARS-CoV-2 status at time of vaccination based on serology and/or PCR	2233 (10.2)	2166 (9.9)	4399 (10.0)
Major protocol deviation evaluated to possibly impact efficacy	33 (0.2)	36 (0.2)	69 (0.2)
In/exclusion criteria	18 (0.1)	23 (0.1)	41 (0.1)
Received wrong treatment or incorrect dose	9 (<0.1)	11 (0.1)	20 (<0.1)
Received a disallowed concomitant medication	2 (<0.1)	2 (<0.1)	4 (<0.1)
Other	4 (<0.1)	1 (<0.1)	5 (<0.1)
Per-protocol set	19630 (89.7)	19691 (90.0)	39321 (89.8)
Participants with at least 8 weeks follow-up[b]	10715 (54.6)	10776 (54.7)	21491 (54.7)
Discontinued from study[b]	41 (0.2)	89 (0.5)	130 (0.3)
Reason for discontinuation[b]			
Withdrawal by participant	30 (0.2)	62 (0.3)	92 (0.2)
Death	1 (<0.1)	11 (0.1)	12 (<0.1)

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Lost to follow-up	6 (<0.1)	4 (<0.1)	10 (<0.1)
Physician decision	2 (<0.1)	1 (<0.1)	3 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Other	2 (<0.1)	10 (0.1)	12 (<0.1)
Participants included in per-protocol set until treatment unblinding[b]	1046 (5.3)	1138 (5.8)	2184 (5.6)

Source: Sponsor table TSIDS02_A
[a] These values are denominators for the percentage calculations
[b] Based on the per-protocol set

The table below summarizes the disposition of the safety analysis population. In the FAS, 54.6% of participants completed at least 8 weeks follow-up. The proportion of participants who discontinued from the study was 0.3% (n=145) across study groups, with a greater number in the placebo group (n=96) compared with the vaccine group (n=49). The most frequently reported reason was withdrawal by participant. In the safety subset, almost all (99.9%) participants completed assessments through 29 days post-vaccination. As of the data cutoff date of January 22, 2021, in the FAS, 4.9% of participants in the vaccine group and 5.4% of participants in the placebo group were unblinded due to request by participant after the participant became eligible to receive an authorized COVID-19 vaccine under EUA.

Table 5. Disposition, Safety Analysis Population, Study 3001

Disposition	Ad26.COV2.S n (%)	Placebo n (%)	Total n (%)
Randomized	22174	22151	44325
Vaccinated[a]	21895	21888	43783
Vaccinated with incorrect vaccine	6	5	11
Full analysis set	21895 (100.0)	21888 (100.0)	43783 (100.0)
Participants with at least 8 weeks follow-up	11948 (54.6)	11955 (54.6)	23903 (54.6)
Participants unblinded to treatment	1080 (4.9)	1177 (5.4)	2257 (5.2)
Discontinued from study	49 (0.2%)	96 (0.4%)	145 (0.3)
Reason for discontinuation			
Withdrawal by participant	35 (0.2)	66 (0.3)	101 (0.2)
Death	2 (<0.1)	12 (0.1)	14 (<0.1)
Lost to follow-up	6 (<0.1)	5 (<0.1)	11 (<0.1)
Physician decision	2 (<0.1)	1 (<0.1)	3 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Other	4 (<0.1)	11 (0.1)	15 (<0.1)
Safety subset	3356 (15.3)	3380 (15.4)	6736 (15.4)
Completed post-vaccination (Day 1-29)[b]	3354 (99.9)	3376 (99.9)	6730 (99.9)

[a] These values are denominators for the percentage calculations
[b] Percentage based on Safety subset

4.2.5 Demographics and Other Baseline Characteristics

In the per-protocol set, 44.5% of participants were female and 20.4% were ≥65 years of age. Overall, 62.1% of participants were white, 17.2% Black or African American, 8.3% American Indian or Alaska Native, 3.5% Asian, 0.3% Native Hawaiian or other Pacific Islander, and 5.4% multiracial; 45.1% of participants were Hispanic/Latino. At least one comorbidity was present for 39.9% of participants. Geographically, 46.7% of subjects participated in the United States, 17.3% in Brazil, 12.7% in South Africa, and the remaining 23.3% in 5 different countries in Latin America. Baseline demographics in U.S. participants included in the study were similar to that of

the global demographics, with the exception of lower percentages of participants who were American Indian or Alaska Native (1.0%) and participants who identified as Hispanic or Latino (14.2%). There was a similar distribution of demographic characteristics between the treatment groups.

Table 6. Demographic Characteristics, Per-Protocol Set, Study 3001

Subgroup	Ad26.COV2.S	Placebo	All Participants
Per-protocol set	**19630**	**19691**	**39321**
Age (years)			
Mean (SD)	51.1 (15.0)	51.2 (15.0)	51.1 (15.0)
Median	52.0	53.0	53.0
Range	(18, 100)	(18, 94)	(18, 100)
Age group (years)			
18-59	12830 (65.4%)	12881 (65.4%)	25711 (65.4%)
≥60	6800 (34.6%)	6810 (34.6%)	13610 (34.6%)
≥65	3984 (20.3%)	4018 (20.4%)	8002 (20.4%)
≥75	755 (3.8%)	693 (3.5%)	1448 (3.7%)
Sex			
Female	8702 (44.3%)	8777 (44.6%)	17479 (44.5%)
Male	10924 (55.6%)	10910 (55.4%)	21834 (55.5%)
Undifferentiated	2 (<0.1%)	4 (<0.1%)	6 (<0.1%)
Unknown	2 (<0.1%)	0	2 (<0.1%)
Race			
American Indian or Alaska Native	1643 (8.4%)	1628 (8.3%)	3271 (8.3%)
Asian	720 (3.7%)	663 (3.4%)	1383 (3.5%)
Black or African American	3374 (17.2%)	3390 (17.2%)	6764 (17.2%)
Native Hawaiian or other Pacific Islander	54 (0.3%)	45 (0.2%)	99 (0.3%)
White	12200 (62.1%)	12216 (62.0%)	24416 (62.1%)
Multiple	1036 (5.3%)	1087 (5.5%)	2123 (5.4%)
Unknown	603 (3.1%)	662 (3.4%)	1265 (3.2%)
Ethnicity			
Hispanic or Latino	8793 (44.8%)	8936 (45.4%)	17729 (45.1%)
Not Hispanic or Latino	10344 (52.7%)	10259 (52.1%)	20603 (52.4%)
Unknown	493 (2.5%)	496 (2.5%)	989 (2.5%)
Region and Country			
Latin America	7967 (40.6%)	8014 (40.7%)	15981 (40.6%)
Brazil	3399 (17.3%)	3390 (17.2%)	6789 (17.3%)
Chile	531 (2.7%)	540 (2.7%)	1071 (2.7%)
Argentina	1402 (7.1%)	1414 (7.2%)	2816 (7.2%)
Colombia	1858 (9.5%)	1869 (9.5%)	3727 (9.5%)
Peru	571 (2.9%)	581 (3.0%)	1152 (2.9%)
Mexico	206 (1.0%)	220 (1.1%)	426 (1.1%)
Northern America	9185 (46.8%)	9171 (46.6%)	18356 (46.7%)
United States	9185 (46.8%)	9171 (46.6%)	18356 (46.7%)
Southern Africa	2478 (12.6%)	2506 (12.7%)	4984 (12.7%)
South Africa	2478 (12.6%)	2506 (12.7%)	4984 (12.7%)
Presence of baseline comorbidity			
One or more	7830 (39.9%)	7867 (40.0%)	15697 (39.9%)
None	11800 (60.1%)	11824 (60.0%)	23624 (60.1%)

Source: Sponsor table TSIDEM01_A

The demographic characteristics among vaccine and placebo participants in the FAS were similar. There were no significant imbalances in demographic or other baseline characteristics between the per-protocol set and FAS. Overall, 9.6% of vaccinated participants in the study had evidence of previous infection with SARS-CoV-2 at baseline, as assessed by serology prior to vaccination.

Table 7. Demographic Characteristics, Full Analysis Set, Study 3001

Subgroup	Ad26.COV2.S	Placebo	All Participants
Full analysis set	**21895**	**21888**	**43783**
Age (years)			
Mean (SD)	50.7 (15.1)	50.7 (15.0)	50.7 (15.1)
Median	52.0	52.0	52.0
Range	(18, 100)	(18, 94)	(18, 100)
Age group			
18-59	14564 (66.5%)	14547 (66.5%)	29111 (66.5%)
≥60	7331 (33.5%)	7341 (33.5%)	14672 (33.5%)
≥65	4259 (19.5%)	4302 (19.7%)	8561 (19.6%)
≥75	809 (3.7%)	732 (3.3%)	1541 (3.5%)
Sex			
Female	9820 (44.9%)	9902 (45.2%)	19722 (45.0%)
Male	12071 (55.1%)	11982 (54.7%)	24053 (54.9%)
Undifferentiated	2 (<0.1%)	4 (<0.1%)	6 (<0.1%)
Unknown	2 (<0.1%)	0	2 (<0.1%)
Race			
American Indian or Alaska Native	2083 (9.5%)	2060 (9.4%)	4143 (9.5%)
Asian	743 (3.4%)	687 (3.1%)	1430 (3.3%)
Black or African American	4251 (19.4%)	4264 (19.5%)	8515 (19.4%)
Native Hawaiian or other Pacific Islander	58 (0.3%)	48 (0.2%)	106 (0.2%)
White	12858 (58.7%)	12838 (58.7%)	25696 (58.7%)
Multiple	1204 (5.5%)	1245 (5.7%)	2449 (5.6%)
Unknown	308 (1.4%)	315 (1.4%)	623 (1.4%)
Ethnicity			
Hispanic or Latino	9874 (45.1%)	9963 (45.5%)	19837 (45.3%)
Not Hispanic or Latino	11472 (52.4%)	11362 (51.9%)	22834 (52.2%)
Unknown	197 (0.9%)	199 (0.9%)	396 (0.9%)
Region and country			
Latin America	8954 (40.9%)	8951 (40.9%)	17905 (40.9%)
Argentina	1498 (6.8%)	1498 (6.8%)	2996 (6.8%)
Brazil	3644 (16.6%)	3634 (16.6%)	7278 (16.6%)
Chile	563 (2.6%)	570 (2.6%)	1133 (2.6%)
Colombia	2125 (9.7%)	2123 (9.7%)	4248 (9.7%)
Mexico	238 (1.1%)	241 (1.1%)	479 (1.1%)
Peru	886 (4.0%)	885 (4.0%)	1771 (4.0%)
Northern America	9655 (44.1%)	9647 (44.1%)	19302 (44.1%)
United States	9655 (44.1%)	9647 (44.1%)	19302 (44.1%)
Southern Africa	3286 (15.0%)	3290 (15.0%)	6576 (15.0%)
South Africa	3286 (15.0%)	3290 (15.0%)	6576 (15.0%)

Subgroup	Ad26.COV2.S	Placebo	All Participants
Full analysis set	**21895**	**21888**	**43783**
SARS-CoV-2 serostatus status at baseline			
Positive	2151 (9.8%)	2066 (9.4%)	4217 (9.6%)
Negative	19104 (87.3%)	19191 (87.7%)	38295 (87.5%)
Missing	640 (2.9%)	631 (2.9%)	1271 (2.9%)
Presence of baseline comorbidity			
One or more	8936 (40.8%)	8922 (40.8%)	17858 (40.8%)
None	12959 (59.2%)	12966 (59.2%)	25925 (59.2%)

Source: Sponsor table TSIDEM01_B

The following table provides the proportions of participants with one or more comorbidities associated with an increased risk of progression to severe COVID-19. In the FAS, 40.8% of participants had one or more comorbidities at baseline. The most common comorbidities were obesity (28.5%) and hypertension (10.3%). The study also included participants who were HIV positive (2.8%). The proportions of individuals with comorbidities were similar between the vaccine and placebo groups and between the FAS and per-protocol set.

Table 8. Participants With Comorbidities, Full Analysis Set, Study 3001

Baseline Comorbidity Category	Ad26.COV2.S (N=21895) n (%)	Placebo (N=21888) n (%)	Total (N=43783) n (%)
No comorbidity	12959 (59.2)	12966 (59.2)	25925 (59.2)
With one or more comorbidity	8936 (40.8)	8922 (40.8)	17858 (40.8)
Asthma	262 (1.2)	300 (1.4)	562 (1.3)
Cancer	112 (0.5)	114 (0.5)	226 (0.5)
Cerebrovascular disease	78 (0.4)	80 (0.4)	158 (0.4)
Cystic fibrosis	1 (<0.1)	3 (<0.1)	4 (<0.1)
Chronic kidney disease	112 (0.5)	118 (0.5)	230 (0.5)
COPD	231 (1.1)	206 (0.9)	437 (1.0)
Serious heart conditions	497 (2.3)	511 (2.3)	1008 (2.3)
HIV infection[a]	601 (2.7)	617 (2.8)	1218 (2.8)
Hypertension[b]	2225 (10.2)	2296 (10.5)	4521 (10.3)
Immunocompromised state from blood transplant	43 (0.2)	36 (0.2)	79 (0.2)
Immunocompromised state from organ transplant	7 (<0.1)	3 (<0.1)	10 (<0.1)
Liver disease	103 (0.5)	103 (0.5)	206 (0.5)
Neurologic conditions	82 (0.4)	125 (0.6)	207 (0.5)
Obesity[c]	6277 (28.7)	6215 (28.4)	12492 (28.5)
Pulmonary fibrosis	10 (<0.1)	9 (<0.1)	19 (<0.1)
Sickle cell disease	13 (0.1)	5 (<0.1)	18 (<0.1)
Type 1 diabetes mellitus	105 (0.5)	90 (0.4)	195 (0.4)
Type 2 diabetes mellitus	1600 (7.3)	1594 (7.3)	3194 (7.3)
Thalassemia	16 (0.1)	30 (0.1)	46 (0.1)

Source: Sponsor table TSIDEM01_B

[a] HIV status not collected for participants with no-comorbidities and no medical history of HIV

[b] >150 mm Hg systolic and/or >95 mm Hg diastolic

[c] body mass index >30 kg/m^2

Participants in the safety subset were enrolled from 45 sites in 3 Tier 1 countries (US, Brazil and South Africa). The Tier 1 countries were selected based on rapid start-up capacity and projected incidence rates for COVID-19 that would allow for rapid efficacy signal detection. At the site level, investigators questioned participants on their willingness to be part of the safety subset.

Selection and randomization of the participants was then completed through a web-based randomization system. In safety subset, 48.3% of participants were female, and 23.0% were ≥65 years of age, which is similar to the FAS. A larger percentage of participants in the safety subset were white (83.4%) compared to the FAS (58.7%). Geographically, the safety subset was limited to participants in the United States (51.4%), South Africa (10.2%), and Brazil (38.5%). Fewer participants in the safety subset compared to the FAS were seropositive at baseline (4.5% versus 9.6%) and had a least one comorbidity (34.1% versus 40.8%).

Table 9. Demographic Characteristics, Safety Subset, Study 3001

Subgroup	Ad26.COV2.S	Placebo	Total
Safety Subset	**3356**	**3380**	**6736**
Age (years)			
Mean (SD)	51.4 (15.9)	51.1 (16.1)	51.2 (16.0)
Median	54.0	54.0	54.0
Range	(18, 90)	(18, 91)	(18, 91)
Age group (years)			
18-59	2036 (60.7%)	2049 (60.6%)	4085 (60.6%)
≥60	1320 (39.3%)	1331 (39.4%)	2651 (39.4%)
≥65	763 (22.7%)	786 (23.3%)	1549 (23.0%)
≥75	150 (4.5%)	138 (4.1%)	288 (4.3%)
Sex			
Female	1637 (48.8%)	1615 (47.8%)	3252 (48.3%)
Male	1719 (51.2%)	1765 (52.2%)	3484 (51.7%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race			
American Indian or Alaska Native	9 (0.3%)	9 (0.3%)	18 (0.3%)
Asian	114 (3.4%)	105 (3.1%)	219 (3.3%)
Black or African American	267 (8.0%)	260 (7.7%)	527 (7.8%)
Native Hawaiian or other Pacific Islander	9 (0.3%)	10 (0.3%)	19 (0.3%)
White	2798 (83.4%)	2823 (83.5%)	5621 (83.4%)
Multiple	97 (2.9%)	112 (3.3%)	209 (3.1%)
Unknown	20 (0.6%)	17 (0.5%)	37 (0.5%)
Ethnicity			
Hispanic or Latino	1284 (38.3%)	1287 (38.1%)	2571 (38.2%)
Not Hispanic or Latino	2024 (60.3%)	2038 (60.3%)	4062 (60.3%)
Unknown	12 (0.4%)	14 (0.4%)	26 (0.4%)
Region and country			
Latin America	1291 (38.5%)	1299 (38.4%)	2590 (38.5%)
Argentina	0	0	0
Brazil	1291 (38.5%)	1299 (38.4%)	2590 (38.5%)
Chile	0	0	0
Colombia	0	0	0
Mexico	0	0	0
Peru	0	0	0
Northern America	1727 (51.5%)	1735 (51.3%)	3462 (51.4%)
United States	1727 (51.5%)	1735 (51.3%)	3462 (51.4%)
Southern Africa	338 (10.1%)	346 (10.2%)	684 (10.2%)
South Africa	338 (10.1%)	346 (10.2%)	684 (10.2%)

Subgroup	Ad26.COV2.S	Placebo	Total
Safety Subset	**3356**	**3380**	**6736**
SARS-CoV-2 serostatus status at baseline			
Positive	154 (4.6%)	147 (4.3%)	301 (4.5%)
Negative	3117 (92.9%)	3129 (92.6%)	6246 (92.7%)
Missing	85 (2.5%)	104 (3.1%)	189 (2.8%)
Presence of baseline comorbidity			
One or more	1135 (33.8%)	1164 (34.4%)	2299 (34.1%)
None	2221 (66.2%)	2216 (65.6%)	4437 (65.9%)

Source: Sponsor table TSIDEM01_D

4.2.6 Vaccine Efficacy

Primary Efficacy Analysis

The primary efficacy analysis was based on the per-protocol set, which consisted of all vaccinated participants who were SARS-CoV-2 seronegative at time of vaccination and who had no major protocol deviations. The co-primary efficacy endpoints were vaccine efficacy (VE) in preventing protocol-defined moderate to severe/critical COVID-19, confirmed by the central laboratory, occurring at least 14 days and at least 28 days after vaccination, respectively. The primary efficacy success criterion would be met if the null hypothesis of VE ≤30% is rejected and the VE point estimate is ≥50% for both co-primary endpoints at the primary analysis. As shown in Table 10, in participants ≥18 years of age, VE against moderate to severe/critical COVID-19 with onset at least 14 days after vaccination was 66.9% (a lower bound of the 95% CI of 59.03), and VE against moderate to severe/critical COVID-19 with onset at least 28 days after vaccination was 66.1% (a lower bound of 95% CI of 55.01), which together met the pre-specified success criteria. Vaccine efficacy was similar between the two age groups of participants 18 to 59 and ≥60 years of age.

Table 10. Vaccine Efficacy Against Centrally Confirmed Moderate to Severe/Critical COVID-19 With Onset at Least 14 and at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Co-primary Endpoint Subgroup	**Ad26.COV2.S Cases (N)[a] Person-yrs[b]**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**
All participants	116 (19514) 3116.6	348 (19544) 3096.1	66.9% (59.0, 73.4)	66 (19306) 3102.0	193 (19178) 3070.7	66.1% (55.0, 74.8)
Age 18-59 years	95 (12750) 2106.8	260 (12782) 2095.0	63.7% (53.9, 71.6)	52 (12617) 2097.6	152 (12527) 2077.0	66.1% (53.3, 75.8)
Age ≥60 years	21 (6764) 1009.8	88 (6762) 1001.2	76.3% (61.6, 86.0)	14 (6689) 1004.4	41(6651) 993.6	66.2% (36.7, 83.0)

Source: Sponsor tables GEFPE02_A and GEFPE02_C

[a] N=Total number of participants at risk per category

[b] Person-years include time from vaccination to the onset of moderate to severe/critical COVID-19, discontinuation from study, major protocol deviation, unblinding to receive alternative vaccine, or data cutoff, whichever comes first.

Due to the high incidence rate of COVID-19 during the study, not all positive PCR tests had been confirmed by the central laboratory at the time of data cutoff. Of 682 primary endpoint cases with positive PCR from any lab accrued at the time of the data cutoff date, 464 were centrally confirmed. The statistical analysis plan specified that the primary and secondary endpoints would be based on centrally confirmed COVID-19, and thus only centrally confirmed cases were included in analyses of vaccine efficacy. For the subgroup analyses for the primary and secondary endpoints, positive PCR results from any source were used to increase the

number of cases and the precision of the estimate. At the time of the data cutoff, there was high concordance between all local and central laboratory PCR results (90.3%). Evaluation of the primary efficacy endpoint including non-centrally-confirmed cases yielded results similar to those reported above (66.3% and 65.5% for onset at least 14 days and at least 28 days after vaccination, respectively). On February 12, the Sponsor submitted an update on centrally confirmed cases as an amendment to the EUA request; based on cases accrued by the time of the data cutoff and analyzed by the central laboratory by February 8, 582 primary endpoint cases were centrally confirmed. Vaccine efficacy based on this updated dataset was similar to that reported above (67.4% and 66.2% for onset at least 14 days and at least 28 days after vaccination, respectively). The high rate of concordance between local and central lab PCR tests and similar co-primary analysis results regardless of inclusion or exclusion of non-centrally confirmed cases support the inclusion of cases awaiting central laboratory confirmation in subgroup analyses to increase their robustness and improve interpretability.

The demographics of participants with moderate to severe/critical COVID-19, including non-centrally confirmed cases, with onset at least 14 days after vaccination are displayed below. The majority of COVID-19 cases were among participants in the United States, South Africa, and Brazil. Study participants with comorbidities were not over-represented among COVID-19 cases as compared to the overall study population.

Table 11. Demographic Characteristics of Participants With Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 days After Vaccination, Per-Protocol Set

Subgroup	Ad26.COV2.S N (%)	Placebo N (%)	All Participants N (%)
All participants	**173**	**509**	**682**
Age group (years)			
18-59	137 (79.2%)	389 (76.4%)	526 (77.1%)
≥60	36 (20.8%)	120 (23.6%)	156 (22.9%)
Sex			
Female	88 (50.9%)	240 (47.2%)	328 (48.1%)
Male	85 (49.1%)	269 (52.9%)	354 (51.9%)
Race			
American Indian or Alaska Native	21 (12.1%)	41 (8.1%)	62 (9.1%)
Asian	6 (3.5%)	12 (2.4%)	18 (2.6%)
Black or African American	37 (21.4%)	101 (19.8%)	138 (20.2%)
Native Hawaiian or other Pacific Islander	1 (0.6%)	0 (0.0%)	1 (0.2%)
White	94 (54.3%)	288 (56.6%)	382 (56.0%)
Multiple	10 (5.8%)	48 (9.4%)	58 (8.5%)
Unknown/ not reported	4 (2.3%)	19 (3.7%)	23 (3.4%)
Ethnicity			
Hispanic or Latino	81 (46.8%)	237 (46.6%)	318 (46.6%)
Not Hispanic or Latino	88 (50.9%)	257 (50.5%)	345 (50.6%)
Unknown/ not reported	4 (2.3%)	15 (3.0%)	19 (2.8%)

Subgroup	Ad26.COV2.S N (%)	Placebo N (%)	All Participants N (%)
All participants	**173**	**509**	**682**
Country			
United States	51 (29.5%)	196 (38.5%)	247 (36.2%)
South Africa	43 (24.9%)	90 (17.7%)	133 (19.5%)
Brazil	39 (22.5%)	114 (22.4%)	153 (22.4%)
Colombia	22 (12.7%)	62 (12.2%)	84 (12.3%)
Argentina	8 (4.6%)	30 (5.9%)	38 (5.6%)
Peru	7 (4.1%)	13 (2.6%)	20 (2.9%)
Chile	2 (1.2%)	4 (0.8%)	6 (0.9%)
Mexico	1 (0.6%)	0 (0.0%)	1 (0.2%)
Presence of baseline comorbidity			
None	103 (59.5%)	315 (61. 9%)	418 (61.3%)
One or more	70 (40.5%)	194 (38.1%)	264 (38.7%)
Obesity	51 (29.5%)	151 (29.7%)	202 (29.6%)
Hypertension	14 (8.1%)	38 (7.5%)	52 (7.6%)
Type 2 diabetes mellitus	15 (8.7%)	32 (6.3%)	47 (6.9%)
Serious heart condition	3 (1.7%)	13 (2.6%)	16 (2.4%)
Asthma	1 (0.6%)	9 (1.8%)	10 (1.5%)
HIV infection	5 (2.9%)	5 (1.0%)	10 (1.5%)
COPD	1 (0.6%)	5 (1.0%)	6 (0.9%)
Liver disease	1 (0.6%)	2 (0.4%)	3 (0.4%)
Cancer	0 (0.0%)	2 (0.4%)	2 (0.3%)
Immunocompromised from blood transplant	2 (1.2%)	0 (0.0%)	2 (0.3%)
Neurologic conditions	0 (0.0%)	1 (0.2%)	1 (0.2%)

Source: Sponsor response to IR 17

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the co-primary efficacy endpoints provide additional information on the applicability of these results across the general population. For the subgroup analyses, cases with any positive PCR, including those still awaiting confirmation by the central laboratory, were included. In general, VE among the subgroups are similar to the VE in the overall study population. The VE results for subgroups with small numbers of participants (e.g., participants ≥75 years of age, certain racial subgroups) have limited interpretability but are displayed for completeness.

Table 12. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Demographic Characteristics, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Sex						
Male	85 (10861) 1739.0	269 (10832) 1715.9	68.8% (60.1, 75.9)	54 (10764) 1732.4	176 (10649) 1704.2	69.8% (58.9, 78.2)
Female	88 (8649) 1374.2	240 (8708) 1372.6	63.4% (53.1, 71.7)	59 (8538) 1367.1	148 (8525) 1361.1	60.3% (46.0, 71.2)

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**
Age group (yrs)						
18-64	157 (15544) 2527.8	441 (15552) 2504.8	64.7% (57.6, 70.8)	101 (15378) 2517.1	286 (15253) 2485.9	65.1% (56.1, 72.5)
≥65	16 (3970) 586.1	68 (3992) 584.3	76.5% (59.1, 87.3)	12 (3928) 583.1	38 (3925) 580.0	68.6% (38.6, 85.1)
≥75	1 (751) 107.3	9 (690) 99.1	89.7% (26.0, 99.8)	0 (740) 106.4	4 (673) 98.0	
Race						
Amer. Indian/ Alaskan	21 (1634) 279.0	41 (1621) 275.4	49.4% (12.4, 71.6)	18 (1628) 278.4	26 (1604) 274.4	31.7% (-29.4, 64.8)
Asian	6 (714) 99.5	12 (649) 90.6	54.4% (-31.1, 86.0)	2 (689) 97.9	7 (626) 89.1	74.0% (-36.5, 97.4)
Black or African Amer.	37 (3362) 495.7	101 (3361) 491.4	63.7% (46.6, 75.8)	21 (3330) 493.7	66 (3300) 487.3	68.6% (48.0, 81.8)
Native Hawaiian/ Other	1 (54) 8.0	0 (44) 6.6		1 (54) 8.0	0 (43) 6.6	
White	94 (12123) 1975.4	288 (12133) 1958.3	67.6% (59.0, 74.6)	64 (11994) 1967.0	187 (11912) 1944.4	66.2% (54.8, 74.9)
Multiple	10 (1028) 166.6	48 (1080) 170.8	78.6% (57.3, 90.4)	4 (1018) 166.0	28 (1055) 169.2	85.4% (58.4, 96.3)
Ethnicity						
Hispanic/ Latino	81 (8733) 1418.6	237 (8869) 1429.3	65.6% (55.5, 73.6)	59 (8688) 1415.7	153 (8741) 1421.4	61.3% (47.4, 71.8)
Not Hispanic/ Latino	88 (10289) 1620.3	257 (10184) 1587.7	66.4% (57.1, 74.0)	52 (10131) 1610.1	163 (9957) 1573.1	68.8% (57.2, 77.6)
Region						
Northern America (U.S.)	51 (9119) 1414.0	196 (9086) 1391.3	74.4% (65.0, 81.6)	32 (8958) 1403.4	112 (8835) 1375.6	72.0% (58.2, 81.7)
Southern Africa (South Africa)	43 (2473) 377.6	90 (2496) 379.2	52.0% (30.3, 67.4)	23 (2449) 376.1	64 (2463) 376.9	64% (41.2, 78.7)
Latin America	79 (7922) 1322.2	223 (7962) 1318.5	64.7% (54.1, 73.0)	58 (7899) 1320.8	148 (7880) 1313.3	61.0% (46.9, 71.8)

N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
Source: Sponsor tables GEFPE09A, GEFPE09C

Additional subgroup analyses were conducted to evaluate vaccine efficacy by risk factor for severe COVID-19. Vaccine efficacy against moderate to severe/critical COVID-19 with onset at least 28 days after vaccination was lower for individuals with comorbid conditions than for those without such conditions, especially in the subgroup of participants ≥60 years of age. However, the confidence intervals are wide, and the uncertainty of the point estimate is large, as shown in Table 13. The wide confidence intervals for the ≥28 days endpoint are attributable to lower

numbers of cases due to the relatively shorter follow up duration (median of approximately 7 weeks) and with a greater proportion of participants in this subgroup who were unblinded (6.0% compared to 4.4% for 18-59 years cohort overall) due to eligibility for authorized COVID-19 vaccine under EUA, smaller number of participants, and lower incidence of COVID-19 in the cohort of those ≥60 years with comorbidities. For this and several other subgroups, the VE estimate increased and the confidence interval narrowed as the number of cases included in the analysis increased (with inclusion of non-centrally confirmed cases and with cases starting after 14 days), indicating that the apparent lower VE estimates in certain analyses potentially reflect imprecision associated with smaller numbers of cases. For a majority of individual comorbid conditions, interpretation of the results is limited by small sample size and low incidence of COVID-19. However, for subgroups with higher incidence of COVID-19, such as participants with obesity, the VE was similar to the VE estimate in the overall study population.

Table 13. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Risk Factors for Severe COVID-19, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**
Comorbidity, presence						
Yes	70 (7777) 1138.8	194 (7798) 1130.9	64.2% (52.7, 73.1)	44 (7684) 1133.0	105 (7626) 1120.0	58.6% (40.6, 71.6)
No	103 (11737) 1975.1	315 (11746) 1958.2	67.6% (59.4, 74.3)	69 (11622) 1967.3	219 (11552) 1945.9	68.8% (59.0, 76.6)
Age group and comorbidity presence						
18-59, no	89 (8346) 1433.5	258 (8411) 1428.2	65.6% (56.1, 73.3)	58 (8267) 1428.2	180 (8254) 1418.3	68.0% (56.8, 76.6)
18-59, yes	48 (4404) 671.5	131 (4371) 661.0	63.9% (49.4, 74.7)	29 (4350) 668.1	79 (4273) 654.8	64.0% (44.3, 77.3)
≥60, no	14 (3391) 541.6	57 (3335) 530.0	76.0% (56.3, 87.6)	11 (3355) 539.0	39 (3298) 527.6	72.4% (45.0, 87.3)
≥60, yes	22 (3373) 467.4	63 (3427) 469.9	64.9% (42.2, 79.4)	15 (3334) 464.9	26 (3353) 465.2	42.3% (-13.1, 71.6)
Comorbidity, type[b]						
Asthma	1 (238) 34.3	9 (278) 39.5	87.2% (7.6, 99.7)	0 (235) 34.1	4 (270) 38.9	
Cancer	0 (104) 14.2	2 (108) 15.0		0 (102) 14.1	0 (105) 14.8	
Chronic kidney disease	0 (106) 15.1	1 (109) 15.3		0 (102) 14.8	0 (106) 15.1	
COPD	1 (213) 30.2	5 (195) 28.0	81.5% (-65.2, 99.6)	1 (211) 30.1	3 (192) 27.8	
Serious heart conditions	3 (460) 65.3	13 (487) 67.7	76.1% (12.9, 95.6)	1 (455) 64.9	5 (472) 66.8	79.4% (-83.7, 99.6)
HIV infection	5 (467) 69.1	5 (498) 72.4	-4.8% (-355.2, 75.9)	2 (461) 68.7	4 (493) 72.2	47.5% (-266.0, 95.3)

	Onset at Least 14 Days			Onset at Least 28 Days		
Subgroup	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[a] (95% CI)**
Hypertension	14 (1999) 283.3	38 (2019) 282.8	63.2% (30.6, 81.6)	11 (1978) 281.9	17 (1977) 280.2	35.7% (-45.6, 72.8)
Immuno-compromised from blood transplant	2 (38) 4.9	0 (33) 4.6		1 (35) 4.7	0 (32) 4.5	
Liver disease	1 (97) 14.5	2 (100) 14.7		1 (96) 14.4	0 (98) 14.6	
Neurologic conditions	0 (77) 11.1	1 (115) 16.5		0 (77) 11.1	1 (114) 16.5	
Obesity	51 (5383) 794.1	151 (5352) 780.3	66.8% (54.1, 76.3)	30 (5318) 790.0	86 (5223) 772.0	65.9% (47.8, 78.3)
Type 2 diabetes mellitus	15 (1399) 198.7	32 (1410) 199.5	52.9% (10.5, 76.3)	10 (1380) 197.5	13 (1378) 197.7	23.0% (-90.1, 69.8)

Source: Sponsor tables GEFPE09A, GEFPE09C
N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
[b] Results not shown for comorbidities which did not have any cases in either arm for either of the two time periods

Among the 4,156 participants with positive baseline SARS-CoV-2 status who would have otherwise fulfilled the criteria for the per-protocol set, there were 7 moderate to severe/critical COVID-19 cases which occurred at least 14 days post-vaccination (3 in vaccine group, 4 in placebo group), of which 3 cases occurred at least 28 days post-vaccination (1 in vaccine group, 2 in placebo group). One case, in a participant in the vaccine group, was assessed as severe. Of the 7 cases, only one case was centrally confirmed at the time of the data cutoff. There is insufficient data at this time to evaluate vaccine efficacy in previously infected individuals.

Table 14. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical COVID-19, Including Non-centrally Confirmed Cases, With Onset at Least 14 or at Least 28 Days After Vaccination, by Baseline SARS-CoV-2 Status[a], Per-Protocol Set

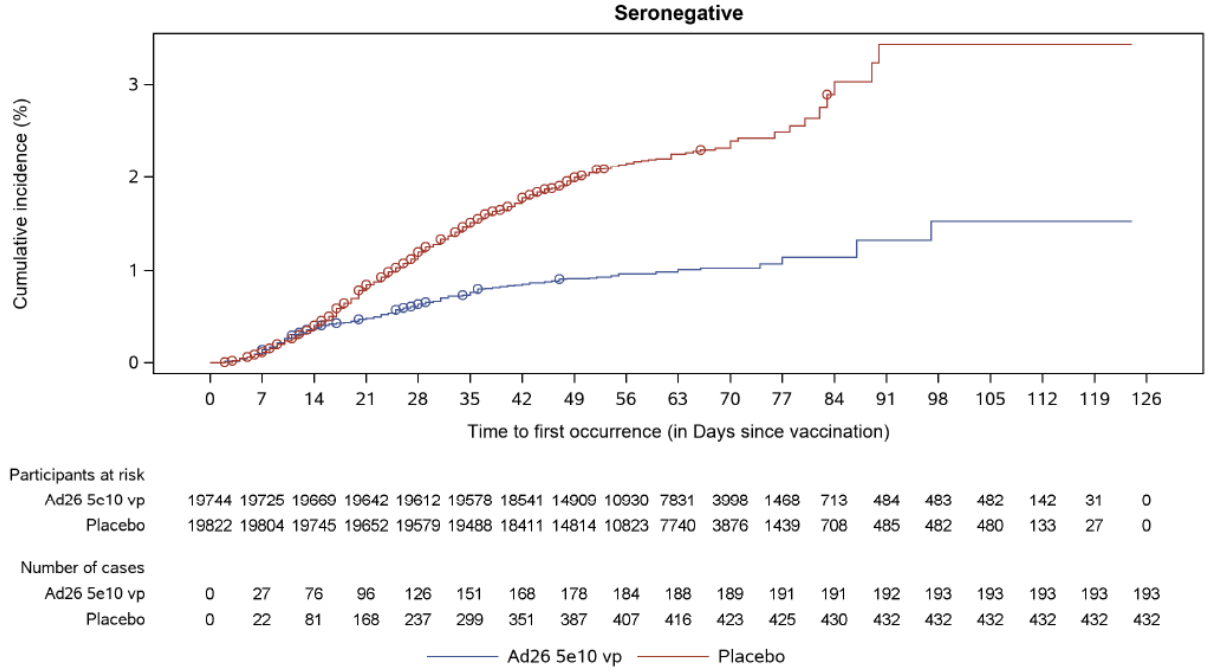
	Onset at Least 14 Days			Onset at Least 28 Days		
Baseline SARS-CoV-2 Serostatus[a]	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE% (95% CI)**	**Ad26.COV2.S Cases (N) Person-yrs**	**Placebo Cases (N) Person-yrs**	**VE%[b] (95% CI)**
Regardless of baseline SARS-CoV-2 status	176 (21636) 3450.2	513 (21574) 3409.8	66.1% (59.7, 71.6)	114 (21424) 3436.3	326 (21199) 3385.9	65.5% (57.2, 72.4)
Positive	3 (2122) 336.3	4 (2030) 320.8	28.5% (-322.8, 89.5)	1 (2118) 336.1	2 (2021) 320.0	
Negative	173 (19514) 3113.9	509 (19544) 3089.1	66.3% (59.9, 71.8)	113 (19306) 3100.3	324 (19178) 3065.9	65.5% (57.2, 72.4)

Source: Sponsor tables GEFPE07A, GEFPE07C
N=Total number of participants at risk per category
[a] Based on serological test at baseline
[b] If fewer than 6 cases are observed for an endpoint then the VE is not shown

Cumulative Incidence Curves –Primary Efficacy Analysis

Cumulative incidence of moderate to severe/critical COVID-19 in the FAS was similar in both the vaccine and placebo groups until around Day 14, following which the curves diverge, with more cases accumulating in the placebo group than the vaccine group.

Figure 1. Cumulative Incidence Curve of Centrally Confirmed Moderate to Severe/Critical COVID-19 Cases With Onset at Least 1 Day After Vaccination, Full Analysis Set



Secondary Efficacy Analyses

Efficacy Against Any Symptomatic COVID-19

Efficacy against any symptomatic COVID-19 (including mild disease) and efficacy based on a less restrictive case definition (FDA harmonized case definition), with onset at least 14 days or 28 days after vaccination, were overall similar to results obtained for the primary efficacy endpoint of efficacy against moderate to severe/critical COVID-19. There were only 4 centrally confirmed mild COVID-19 cases (1 in vaccine group, 3 in placebo group) with onset ≥14 days post-vaccination, indicating that the moderate to severe/critical primary efficacy endpoint definition captured almost all cases of symptomatic COVID-19.

Table 15. Vaccine Efficacy Against Centrally Confirmed COVID-19[a] With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Symptomatic COVID-19, any severity[a]	117 (19514) 3116.5	351 (19544) 3095.9	66.9% (59.1, 73.4)	66 (19306) 3102.0	195 (19178) 3070.5	66.5% (55.5, 75.1)

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
FDA harmonized COVID-19 cases	114 (19514) 3116.6	345 (19544) 3096.3	67.2% (59.3, 73.7)	65 (19306) 3102.0	193 (19178) 3070.6	66.7% (55.6, 75.2)

Source: Sponsor tables TEFSUM01_A, TEMSUM01_C
N=Total number of participants at risk per category
[a] Includes mild, moderate, and severe/critical cases

Severe COVID-19 Cases

All COVID-19 cases which met the severe/critical definition as specified by the study protocol and all moderate cases with a total of 3 or more signs and/or symptoms were assessed independently by a clinical severity adjudication committee. Only cases classified as severe/critical by the adjudication committee are included in the severe/critical endpoint. Table 16 shows efficacy against severe/critical COVID-19 including only centrally confirmed cases and efficacy against severe/critical COVID-19 when non-centrally confirmed cases are also included.

As of the cutoff date for adjudication (January 19, 2021), there were 74 centrally confirmed, adjudicated severe/critical COVID-19 cases with an onset at least 14 days after vaccination and 39 cases with an onset at least 28 days after vaccination. Efficacy against severe disease appears to be greater when cases that occurred before 28 days are excluded. Point estimates of efficacy were lower in participants ≥60 years of age compared to participants 18 to 59 years-old when evaluating only centrally confirmed cases; however, the confidence intervals are wide. When non-centrally confirmed cases were included, the VE estimate for participants ≥60 years of age increased (and the confidence interval narrowed) and was more similar to the VE estimates for 18 to 59 year-olds and the overall population.

Table 16. Vaccine Efficacy Against Adjudicated Severe/Critical COVID-19 With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Centrally confirmed cases[a]						
Overall	14 (19514) 3125.1	60 (19544) 3122.0	76.7% (54.6, 89.1)[b]	5 (19306) 3106.2	34 (19178) 3082.6	85.4% (54.2, 96.9)[b]
18-59 years	8 (12750) 2114.3	41 (12782) 2115.1	80.5% (57.8, 92.1)	2 (12617) 2101.0	24 (12527) 2086.7	91.7% (66.7, 99.1)
≥60	6 (6764) 1010.7	19 (6762) 1006.9	68.5% (18.1, 89.7)	3 (6689) 1005.1	10 (6651) 995.9	70.3% (-15.5, 94.7)

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)
Including non-centrally confirmed cases						
Overall	19 (19514) 3124.7	80 (19544) 3121.0	76.3% (57.9, 87.5)	8 (19306) 3106.0	48 (19178) 3082.0	83.5% (54.2, 96.9)
18-59 years	12 (12750) 2114.0	52 (12782) 2114.5	76.9% (56.2, 88.8)	5 (12617) 2100.9	33 (12527) 2086.3	85.0% (61.2, 95.4)
≥60 years	7 (6764) 1010.7	28 (6762) 1006.4	75.1% (41.7, 90.8)	3 (6689) 1005.1	15 (6651) 995.7	80.2% (30.0, 96.3)

Source: Sponsor tables GEFBO06_A, GEFBO06_C, GEFBO05NC_A, GEFBO05NC_C
N=Total number of participants at risk per category
[a] Endpoint for severe/critical disease as specified in SAP
[b] Adjusted 95% CI

Severe cases which occurred after the cutoff date for adjudication were included in the primary efficacy analysis but were not included as severe/critical cases, which is based on adjudicated cases only.

COVID-19 Requiring Medical Intervention

The endpoint of COVID-19 requiring medical intervention is defined as participant requiring hospitalization, ICU admission, mechanical ventilation, and/or ECMO, linked to objective measures such as decreased oxygenation, X-ray or computed tomography (CT) findings, and linked to any molecularly confirmed, COVID-19 with onset at least 14 days and at least 28 days post-vaccination. This endpoint was collected using the Medical Resource Utilization (MRU) form to be completed by the investigator on Days 3 through 5 and/or Day 29 of the COVID-19 episode. The vaccine appears to offer protection against COVID-19 requiring medical intervention starting at least 14 days post-vaccination. In the vaccine group, there were no COVID-19 cases requiring medical intervention, per MRU forms, after 28 days post-vaccination, compared to 5 such cases in the placebo group counting only centrally confirmed cases (7 cases in the placebo group counting any positive PCR).

Table 17. Vaccine Efficacy of First Occurrence COVID-19 Requiring Medical Intervention Based on MRU, With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE% (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Centrally Confirmed	2 (19514) 3126.9	8 (19544) 3126.1	75.0% (-25.3, 97.4)	0 (19306) 3106.4	5 (19178) 3084.4	
Any positive PCR	2 (19514) 3125.9	14 (19544) 3125.8	85.7% (37.8, 98.4)	0 (19306) 3106.4	7 (19178) 3084.4	100% (31.1, 100.0)

Source: Sponsor tables GEFMI03, GEFMI01, GEFMI01NCA, GEFMI01NCC
N=Total number of participants at risk per category
[a] If fewer than 6 cases are observed for an endpoint then the VE is not shown.
Abbreviation: MRU, Medical Resource Utilization

The Day 29 timepoint included in the MRU forms resulted in some cases requiring medical intervention not having MRU forms returned by the data cutoff date, and these cases were not included in the analysis above. A post hoc analysis of all COVID-19 hospitalizations was performed by counting all hospitalizations recorded in MRU forms, SAEs, and clinical event listings (e.g., during a severe/critical COVID-19 episode), in the setting of a positive PCR at the onset of the COVID-19 episode or onset of the AE. In total, 48 COVID-19 hospitalizations were identified among participants without evidence of SARS-CoV-2 PCR infection at baseline. The totality of these data indicates vaccine efficacy in the prevention of severe COVID-19 requiring hospitalization, with no COVID-19 related hospitalizations in the vaccine group following 28 days after vaccination.

Table 18. Vaccine Efficacy of First Occurrence COVID-19 Requiring Hospitalization, With Onset at Least 14 or at Least 28 Days After Vaccination, Per-Protocol Set, Study 3001 (Post Hoc Analysis)

Onset After Vaccination	Ad26.COV2.S No. of Cases (Person-yrs)	Placebo No. of Cases (Person-yrs)	VE% (95% CI)
At least 1 day (FAS-seronegative at baseline)			
Centrally confirmed	6 (3202.8)	18 (3213.1)	66.6% (12.1, 89.1)
Any positive PCR	6 (3202.8)	42 (3211.6)	85.7% (66.1, 95.0)
At least 14 days			
Centrally confirmed	2 (3125.8)	11 (3125.9)	81.8% (16.7, 98.0)
Any positive PCR	2 (3125.8)	29 (3125.1)	93.1% (72.7, 99.2)
At least 28 days			
Centrally confirmed	0 (3106.3)	6 (3084.4)	100% (15.7, 100.0)
Any positive PCR	0 (3106.3)	16 (3083.9)	100% (74.3, 100.0)

Source: TEFMI04

The 2 COVID-19 related hospitalizations that occurred at least 14 days after vaccination in the vaccine group were both participants ≥60 years of age with comorbidities (obesity and hypertension). In the subgroup of participants ≥60 years with comorbidities, 2 of 22 total moderate to severe/critical COVID-19 cases in vaccine recipients resulted in hospitalization (both prior to 28 days) compared to 11 of 63 moderate to severe/critical cases in placebo recipients (with 5 occurring after 28 days).

COVID-19 Related Deaths

As of February 5, 2021, there were 7 COVID-19-related deaths reported in the study. All participants had a documented positive SARS-CoV-2 RT-PCR around the time of the event, but not all have been centrally confirmed to date. All 7 deaths occurred in the placebo group and were in study sites in South Africa. All of these participants had one or more comorbidities which placed them at higher risk for severe COVID-19. One death was in a participant PCR positive at baseline, who had onset of illness 10 days after vaccination. These results suggest that the vaccine is efficacious against mortality associated with COVID-19. Outcomes related to an exploratory all-cause mortality endpoint are discussed in a separate section below.

Table 19. COVID-19 Related Deaths

Arm	Study Day[c]	Age	Comorbidity
Placebo	15	63	Obesity, Hypertension
Placebo	18[a]	52	Obesity, Diabetes
Placebo	31	54	Obesity, Hypertension, Diabetes, Heart failure
Placebo	38	49	Obesity, Hypertension
Placebo	39	68	Obesity
Placebo	49[b]	60	Obesity
Placebo	55	60	Asthma

[a] Participant with positive SARS-CoV-2 PCR at baseline
[b] Reported after the primary analysis cutoff date of January 22, 2021
[c] Study day of death

Vaccine Efficacy Against Asymptomatic Infections

The secondary endpoint for asymptomatic infection was defined in the protocol as a participant who does not fulfill the criteria for suspected COVID-19 based on signs and symptoms (further specified as no symptoms on the day preceding, the day of, or any time after the positive PCR test) AND has a SARS-CoV-2 positive RT-PCR test result OR develops a positive serology based on a SARS-CoV-2 N-specific immunoglobulin assay (Elecsys®, Roche) during the study. SARS CoV-2 seropositivity by non-S protein was assessed at Day 1 (pre-vaccination), Day 29 (28 days post-vaccination), and Day 71. On manual review of the cases included in this endpoint, the Sponsor identified multiple cases in which the participants were symptomatic 2 days or more prior to the positive PCR or serology test. Manual review identified 2 centrally-confirmed cases in the vaccine group which were classified as asymptomatic based on the statistical analysis plan (SAP) but would meet the moderate case definition, and one centrally-confirmed SAP-classified asymptomatic case in the placebo group which would meet the mild case definition, with onset after 14 days post-vaccination. These cases were not included in the primary or secondary efficacy analyses, which are based on SAP-defined cases, but are not expected to significantly change the efficacy results. To remove possibly symptomatic COVID-19 cases from the analysis of asymptomatic infection, the Sponsor conducted a post hoc analysis including only participants without COVID-19 symptoms since screening.

As specified in the SAP, the secondary endpoint of efficacy against all SARS-CoV-2 infection with onset from Day 29 (including asymptomatic infection) will only be tested when at least 15,000 participants with Day 71 serology are available, and the secondary endpoint of efficacy against asymptomatic or undetected infection with onset from Day 29 will only be tested when all participants have at least 6 months of follow-up.

From Day 1 through Day 29, the data show only modest, non-statistically significant vaccine efficacy against asymptomatic SARS-CoV-2 infection. Analysis of the Day 29 and after timepoint shown below is based on an interim analysis of Day 71 serology results from 2,892 participants. These individuals represent 28.8% of the 10,045 participants who had completed the Day 71 visit by the data cutoff date of January 22 (serology results cutoff February 8). The percentage of available serology results are not evenly distributed across study sites (range: 16.9% of study participants in Chile to 68.4% of participants in South Africa). Although these results may suggest potential efficacy against asymptomatic infection after Day 29, this observation should be interpreted with caution as follow-up time is limited, and only a small percentage of participants had available N-serology data to contribute to this endpoint. This analysis was also done at an interim time point not pre-specified by the SAP.

Table 20. Vaccine Efficacy Against Asymptomatic SARS-CoV-2 Infections, Full Analysis Set

	Day 1-Day 29			After Day 29[e]		
	Ad26.COV2.S No. of Cases (Person-yrs)	**Placebo No. of Cases (Person-yrs)**	**VE% (95% CI)**	**Ad26.COV2.S No. of Cases (Person-yrs)**	**Placebo No. of Cases (Person-yrs)**	**VE% (95% CI)**
FAS seronegative at baseline	N=19739	N=19809		N=19301	N=19162	
+PCR and/or serology[b]	159 (1561.3)	182 (1564.1)	12.5% (-8.9, 29.7)	22 (3099.7)	54 (3064.2)	59.7% (32.8; 76.6)
+PCR and/or serology without previous symptoms[b,d]	87 (1556.2)	109 (1559.3)	20.0% (-7.0, 40.4)	10 (3098.0)	38 (3061.5)	74.0% (46.8; 88.4)
Serology risk set[a]	N=14084	N=14019		N=1346	N=1304	
Seroconverted[c]	153 (1114.3)	175 (1108.2)	13.1% (-8.6, 30.5)	18 (312.2)	50 (298.8)	65.5% (39.9; 81.1)
Seroconverted without previous symptoms[c,d]	84 (1109.4)	108 (1103.7)	22.6% (-3.9, 42.5)	10 (310.9)	37 (296.6)	74.2% (47.1; 88.6)

[a] Serology risk set: Participants with a non-S protein serology result available on Day 29 or Day 71
[b] A participant will be considered to have experienced asymptomatic or undetected COVID-19 if the participant does not fulfil the criteria for suspected COVID-19 based on signs and symptoms as detected by the algorithm described in the SAP; 1) no symptoms on the day before, at or after the PCR positive test and 2) has a SARS-CoV-2 positive RT-PCR/molecular test result or develops a positive serology (non-S protein) test
[c] A participant will be considered serologically converted if the participant develops a positive serology (non-S protein) test without a SARS-CoV-2 positive RT-PCR before the positive serology test irrespective of whether previous symptoms occurred
d A participant is considered without previous symptoms if no COVID-19 symptoms occurred before the positive PCR or serology test at any point in time during the study
[e] N (for at risk set and serology risk set) for >Day 29 analysis based on per-protocol Set
Source: Sponsor tables TEFSUM02B, TEFSUM02C, CSR addendum submitted February 12, 2021

Exploratory Efficacy Analyses

Additional vaccine efficacy analyses were conducted and described below.

Effect on All-Cause Mortality

As of the cutoff date for the primary analysis, 19 deaths were reported in the study. Of these 19 deaths, 6 were related to COVID-19, all in the placebo group. There is suggestion of a positive effect on all-cause mortality; however, the confidence interval is wide, with a lower bound below 0 after 28 days post-vaccination.

Table 21. Effect on All-Cause Mortality, Full Analysis Set

	Ad26.COV2.S N=21895 No. of Cases (Person-yrs)	**Placebo N=21888 No. of Cases (Person-yrs)**	**VE% (95% CI)**
At least 1 day after vaccination[a]	3 (3544.8)	16 (3542.2)	81.3% (34.6, 96.5)
At least 14 days after vaccination	3 (3544.8)	15 (3541.9)	80.0% (29.4, 96.3)
At least 28 days after vaccination	2 (3544.3)	8 (3540.7)	75% (-25.2, 97.4)

[a] Cases in the later timepoints are included in the earlier timepoint
Source: GEFACM01B1, GEFACM01B28, GEFACM01B14

An update on deaths reported from the time period of January 22 to February 5 included an additional 6 deaths. Of these 6 deaths, 2 occurred in the vaccine group and 4 occurred in the

placebo group. One of the cases in the placebo group and none in the vaccine group was related to COVID-19.

Sequencing Data from Centrally Confirmed COVID-19 Cases

During the conduct of Study 3001 (September 21, 2020 through the data cutoff date of January 22, 2021), new SARS-CoV-2 variants emerged in geographical regions where the study took place. In a subgroup analysis of vaccine efficacy against moderate to severe/critical COVID-19 in the United States, South Africa, and Brazil, there was lower efficacy observed in South Africa compared to the United States. Vaccine efficacy against severe/critical COVID-19 was comparably high across the three countries, although there was a wide confidence interval around the point estimates for the United States and Brazil.

Table 22. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical and Severe/Critical COVID-19 Including Non-centrally Confirmed Cases With Onset at Least 14 or at Least 28 Days After Vaccination, by Country of Participation, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Country Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] 95% CI	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
United States						
Moderate to severe/critical	51 (9119) 1414.0	196 (9086) 1391.3	74.4% (65.0, 81.6)	32 (8958) 1403.4	112 (8835) 1375.6	72.0% (58.2, 81.7)
Severe/critical	4 (9119) 1417.2	18 (9086) 1404.8	78.0% (33.1, 94.6)	1 (8958) 1405.2	7 (8835) 1382.2	85.9% (-9.4, 99.7)
South Africa						
Moderate to severe/critical	43 (2473) 377.6	90 (2496) 379.2	52.0% (30.3, 67.4)	23 (2449) 376.1	64 (2463) 376.9	64.0% (41.2, 78.7)
Severe/critical	8 (2473) 380.2	30 (2496) 382.9	73.1% (40.0, 89.4)	4 (2449) 377.0	22 (2463) 379.0	81.7% (46.2, 95.4)
Brazil						
Moderate to severe/critical	39 (3370) 555.7	114 (3355) 548.8	66.2% (51.0, 77.1)	24 (3354) 554.8	74 (3312) 546.1	68.1% (48.8, 80.7)
Severe/critical	2 (3370) 558.9	11 (3355) 556.8	81.9% (17.0, 98.1)	1 (3354) 556.2	8 (3312) 549.8	87.6% (7.8, 99.7)

Source: Sponsor tables GEFPE09A, GEFPE09C, GEFBO05NC_A, GEFBO05NC_C
N=Total number of participants at risk per category

Strain sequencing of COVID-19 cases in Study 3001 to inform the vaccine efficacy analysis by region is ongoing. As of February 12, 2021, 71.7% of centrally confirmed primary analysis cases have been sequenced. In the United States, 73.5% of cases have been sequenced, of which 96.4% were identified as the SARS-CoV-2 Wuhan-H1 variant D614G. In South Africa, 66.9% of cases have been sequenced, of which 94.5% were identified as 20H/501Y.V2 variant (B.1.351). In Brazil, 69.3% of cases have been sequenced, of which 69.4% were identified as variant of the P.2 lineage and 30.6% were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, there were no sequenced cases from the B1.1.7 or P.1 lineages. Because strain sequencing of all COVID-19 cases in the study is incomplete at the time of this analysis, and due to selection bias involved in prioritizing the cases to be sequenced first (moderate to

severe/critical cases, cases with onset at least 14 days after vaccination, samples with viral load >200 copies/mL), vaccine efficacy against specific SARS-CoV-2 variants cannot be evaluated at this time.

Efficacy Summary

The data from the primary efficacy analysis, with a cutoff date of January 22, 2021, and median follow-up for efficacy of 2 months post-vaccination, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent protocol-defined moderate to severe/critical COVID-19 occurring at least 14 days after vaccination was 66.9% (95% CI 59.0; 73.4), and 66.1% (95% CI 55.0; 74.8) for moderate to severe/critical COVID-19 occurring at least 28 days after vaccination, in participants without prior evidence of SARS-CoV-2 infection. Results for the secondary endpoint of vaccine efficacy against protocol-defined symptomatic COVID-19 of any severity (mild, moderate, or severe/critical) were similar to those of the primary endpoint of vaccine efficacy against moderate to severe/critical disease. For prevention of centrally confirmed, adjudicated severe/critical disease, vaccine efficacy (95% CI) was 76.7% (54.6, 89.1) with onset at least 14 days after vaccination and 85.4% (54.2, 96.9) with onset at least 28 days after vaccination. In a post hoc analysis of all COVID-19 related hospitalizations starting 14 days after vaccination, including non-centrally confirmed cases, there were 2 cases in the vaccine group (with no cases after 28 days) compared with 29 cases in the placebo group (with 16 cases after 28 days). The evaluation of vaccine efficacy against asymptomatic disease and its interpretation are limited at this time, since the measurements were performed in a small subset of participants.

Efficacy estimates across demographic subgroups in supportive analyses of primary and secondary endpoints were generally consistent with the efficacy estimates in the overall study population, but the small numbers of participants and cases in certain subgroups (e.g., certain racial subgroups, individual comorbid conditions) limit the interpretability of subgroup-specific efficacy results. Neither age nor presence of comorbidities alone impacted the efficacy estimates for the primary endpoints of moderate to severe/critical COVID-19, with the exception of a lower efficacy estimate for COVID-19 with onset at least 28 days post-vaccination in participants with comorbidities compared to those without comorbidities (Table 10 and Table 13).

The efficacy estimate for moderate to severe/critical COVID-19 with onset at least 28 days post-vaccination was lower for the subgroup of participants ≥60 years of age with comorbidities than for younger participants and participants ≥60 years of age without comorbidities (Table 13). Confidence intervals for efficacy estimates across subgroups generally overlapped, and efficacy estimates in participants ≥60 years of age with comorbidities increased as the number of cases included in the analysis increased (i.e., with inclusion of non-centrally confirmed cases and cases starting at 14 days post-vaccination), indicating that lower efficacy estimates in this subgroup potentially reflect imprecision associated with smaller numbers of cases. Efficacy estimates against centrally confirmed severe/critical COVID-19 were reduced in participants ≥60 years of age as compared to younger participants, but there was no meaningful reduction when cases not yet centrally confirmed were included in the analysis (Table 16). The two hospitalizations in vaccine recipients due to COVID-19 with onset at least 14 days post-vaccination occurred in participants ≥60 years of age with comorbidities (as compared to 11 hospitalizations in placebo recipients ≥60 years of age with comorbidities). No vaccine recipients were hospitalized due to COVID-19 with onset at least 28 days post-vaccination.

To explore the possible impact of circulation of variant strains on vaccine efficacy, a subgroup analysis of vaccine efficacy against moderate to severe/critical and severe/critical COVID-19 was done for the United States, South Africa, and Brazil. There was a lower efficacy against moderate to severe/critical disease endpoints observed in South Africa [52.0% (95% CI 30.3, 67.4) and 64.0% (95% CI 41.2, 78.7) starting 14 days and 28 days after vaccination, respectively] compared to the United States (74.4% (65.0, 81.6) and 72.0% (58.2, 81.7) starting 14 days and 28 days after vaccination, respectively), but vaccine efficacy against severe/critical COVID-19 at the two timepoints were similarly high in all 3 countries. Strain sequencing of COVID-19 cases in the study to inform the vaccine efficacy analysis by region is ongoing. As of February 12, 2021, 71.7% of central laboratory confirmed primary analysis cases have been sequenced. In the U.S., 96.4% of the sequenced cases were identified as the SARS-CoV-2 Wuhan-H1 variant D614G. In South Africa, 94.5% of the sequenced cases were identified as 20H/501Y.V2 variant (B.1.351). In Brazil, 69.4% were identified as variant of the P.2 lineage and 30.6% were identified as the Wuhan-H1 variant D614G. As of February 12, 2021, there were no cases identified from B.1.1.7 or P1 lineages.

4.2.7 Safety

The safety analyses presented in this review are derived from safety data available through the cutoff date of January 22, 2021.

The protocol specified safety monitoring for the following:

- Solicited local and systemic reactions during the 7 days following vaccination in the safety subset (N=6,736)
- Unsolicited AEs during the 28 days following vaccination in the safety subset
- MAAEs during the 6 months following vaccination in the FAS (N=43,783)
- SAEs and AEs leading to study discontinuation for the duration of the study in the FAS

Overall, the proportions of participants with MAAEs, SAEs, and deaths were balanced between the vaccine and placebo groups. Rates of unsolicited AEs were also balanced across treatment groups; however, a greater percentage of participants in the vaccine group had unsolicited AEs considered to be related to the study product. As compared to the placebo group, a greater percentage of participants in the vaccine group experienced local and systemic solicited ARs. Rates of ARs were lower in participants ≥60 years of age compared to participants 18 to 59 years of age. The table below summarizes rates of AEs by treatment group and age group.

Table 23. Participants Reporting at Least One Adverse Event, Among All Participants and by Age Group

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Full analysis set	**N=21895**	**N=21888**
Medically attended adverse event	304/21895 (1.4)	408/21888 (1.9)
18-59 years of age	207/14564 (1.4)	272/14547 (1.9)
≥60 years of age	97/7331 (1.3)	136/7341 (1.9)
Related[b] medically attended adverse events	22/21895 (0.1)	22/21888 (0.1)
18-59 years of age	15/14564 (0.1)	18/14547 (0.1)
≥60 years of age	7/7331 (0.1)	4/7341 (0.1)
Serious adverse event	83/21895 (0.4)	96/21888 (0.4)
18-59 years of age	45/14564 (0.3)	56/14547 (0.4)
≥60 years of age	38/7331 (0.5)	40/7341 (0.5)

Adverse Event Type	Ad26.COV2.S n/N (%)	Placebo n/N (%)
Related[b] serious adverse event	7/21895 (<0.1)	2/21888 (<0.1)[c]
18-59 years of age	4/14564 (<0.1)	1/14547 (<0.1)
≥60 years of age	3/7331 (<0.1)	1/7341 (<0.1)
Deaths	3/21895 (<0.1)	16/21888 (0.1)
18-59 years	1/14564 (<0.1)	7/14547 (<0.1)
≥60 years	2/7331 (<0.1)	9/7341 (0.1)
Related[b] deaths	0	0
AEs leading to study discontinuation	0	0
Safety subset	**N=3356**	**N=3380**
Solicited local adverse reaction	1685/3356 (50.2)	657 /3380 (19.4)
18-59 years of age	1218/2036 (59.8)	413/2049 (20.2)
≥60 years of age	467/1320 (35.4)	244/1331 (18.3)
Grade 3 solicited local adverse reaction[a]	23/3356 (0.7)	6/3380 (0.2)
18-59 years of age	18/2036 (0.9)	4/2049 (0.2)
≥60 years of age	5/1320 (0.4)	2/1331 (0.2)
Solicited systemic adverse reaction	1850/3356 (55.1)	1185/3380 (35.1)
18-59 years of age	1252/2036 (61.5)	745/2049 (36.4)
≥60 years of age	598/1320 (45.3)	440/1331 (33.1)
Grade 3 solicited systemic adverse reaction[a]	61/3356 (1.8)	21/3380 (0.6)
18-59 years of age	47/2036 (2.3)	12/2049 (0.6)
≥60 years of age	14/1320 (1.1)	9/1331 (0.7)
Unsolicited adverse event up to 28 days after vaccination	440/3356 (13.1)	407/3380 (12.0)
18-59 years of age	285/2036 (14.0)	275/2049 (13.4)
≥60 years of age	155/1320 (11.7)	132/1331 (9.9)
Grade 3 unsolicited adverse event	16/3356 (0.5)	16/3380 (0.5)
18-59 years of age	10/2036 (0.5)	10/2049 (0.5)
≥60 years of age	6/1320 (0.5)	6/1331 (0.5)
Grade 4 unsolicited adverse event	3/3356 (0.1)	2/3380 (0.1)
18-59 years of age	2/2036 (0.1)	2/2049 (0.1)
≥60 years of age	1/1320 (0.1)	0/1331 (0.0)
Related[b] unsolicited adverse events	242/3356 (7.2)	154/3380 (4.6)
18-59 years of age	163/2036 (8.0)	96/2049 (4.7)
≥60 years of age	79/1320 (6.0)	58 /1331 (4.4)

Source: Sponsor tables TSFAE04, TSFAE05, TSFAESOLLOC27, TSFAESOLSYS27, TSFAESOL02, TSFAEUNSOL01 & TSFAEUNSOL12.
n = number of participants with specified event; N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[a]There were no reports of Grade 4 solicited adverse reactions
[b] Related as assessed by investigator
[c] 1 participant reported 2 SAEs

The following issues were identified during the safety review:

1. Several reports of solicited reactions and non-serious, unsolicited adverse events were omitted from the analyses due to incorrectly coded start dates. However, the omissions did not have a major impact on the estimated event rates (0% to 0.3% of the safety subset of the respective treatment group) and thus did not impact the safety conclusions.

2. Discrepancies were identified between the number of solicited reactions reported by participants in source documents and the number of events reported by the investigator and included in the datasets upon which the safety analyses were based. In response to an FDA information request, the Sponsor conducted queries of potential missing clinical event data for 210 participants, of which 40% of the queried events were determined to

not meet reporting criteria (e.g., participants who did not experience any solicited symptom during the planned 7-day evaluation period or those who experienced an event with toxicity <grade 1). Other than 44 open queries, the remaining queries resulted in corrected reporting of previously missing clinical event data to the relevant datasets that will be included in final safety analyses with the submission of the licensure application. However, based on FDA evaluation of the impacted data, and the fact that these participants represent a small proportion of the safety subset, the corrected solicited ARs are expected to have a minor impact on the rates submitted by the Sponsor in its EUA request.

Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were assessed across groups and are presented in the tables below stratified by age (18 to 59 years; ≥60 years) for participants in the safety subset (N=6,736). Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema and swelling) and systemic reactions (fatigue, headache, myalgia, nausea and fever).

Local Adverse Reactions

Solicited local ARs were reported at higher rates in vaccine recipients than placebo recipients. The proportions of participants reporting any local AR were 50.2% and 19.4% in vaccine and placebo groups, respectively. The proportions reporting at least one grade 3 local AR were 0.7% and 0.2% in vaccine and placebo groups, respectively. There were no reports of grade 4 local reactions in either group.

The most frequently reported local AR was injection site pain, reported by 48.6% of vaccine recipients and 16.7% of placebo recipients. Grade 3 pain was reported in 0.3% of vaccine recipients and <0.1% of placebo recipients. Erythema (vaccine versus placebo: 7.3% versus 3.9%) and swelling (5.3% versus 1.6%) were reported less frequently.

All local ARs were reported more frequently among younger (18-59 years) than older (≥60 years) participants. Among participants in the vaccine group, injection site pain was reported in 58.6% of 18-59-year-olds and 33.3% of ≥60-year-olds. Erythema and swelling were similarly reported at higher rates among younger than older participants in the vaccine group (Table 24).

Among participants in the vaccine group, the overall rate of local ARs was similar between those who were seronegative for SARS-CoV-2 at baseline (n=3,202) and those who were seropositive at baseline (n=154): 50.0% versus 53.9%. Rates for local ARs by baseline serostatus were as follows (seronegative vs. seropositive): injection site pain 48.4% vs. 53.2%; swelling 5.2% vs. 6.5%; erythema 7.4% vs. 4.5%.

The table below provides rates of local ARs by treatment group and age group.

Table 24. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Vaccination, Safety Subset[a], Study 3001

Adverse Reaction	18-59 Years Ad26.COV2.S N=2036 n (%)	18-59 years Placebo N=2049 n (%)	≥60 Years Ad26.COV2.S N=1320 n (%)	≥60 Years Placebo N=1331 n (%)
Any Local	1218 (59.8%)	413 (20.2%)	467 (35.4%)	244 (18.3%)
Grade 3	18 (0.9%)	4 (0.2%)	5 (0.4%)	2 (0.2%)
Pain[b]	1193 (58.6%)	357 (17.4%)	439 (33.3%)	207 (15.6%)
Grade 3	8 (0.4%)	0	3 (0.2%)	2 (0.2%)
Erythema[c]	184 (9.0%)	89 (4.3%)	61 (4.6%)	42 (3.2%)
Grade 3	6 (0.3%)	2 (0.1%)	1 (0.1%)	0
Swelling[b]	142 (7.0%)	32 (1.6%)	36 (2.7%)	21 (1.6%)
Grade 3	5 (0.2%)	2 (0.1%)	2 (0.2%)	0

Source: Sponsor Table TSFAESOLLOC27
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[b] Pain- Grade 3: any use of Rx pain reliever/prevents daily activity;
[c] Erythema and Swelling/Induration- Grade 3: >100mm;
Note: No grade 4 solicited local adverse reactions were reported.

The median time to onset of local ARs was within 2 days of vaccination, and the median duration was 2 days for erythema and pain and 3 days for swelling. Pain was reported to last greater than 7 days in 2.3% of participants in the vaccine group and 2.1% of participants in the placebo group. Among participants in the vaccine group, erythema and swelling had a duration >7 days in 0.8% and 0.5% of participants, respectively.

The table below provides time to onset and duration of local ARs by treatment group.

Table 25. Time (Days) to Onset and Duration of Solicited Local Adverse Events, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S N=3356	Placebo N=3380
Pain, n (%)	1632 (48.6%)	564 (16.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 67)	2.0 (1, 67)
>7 days duration	38 (2.3%)	14 (2.1%)
Erythema, n (%)	245 (7.3%)	131 (3.9%)
Median time to onset (min, max)	2.0 (1, 7)	1.0 (1, 8)
Median duration (min, max)	2.0 (1, 9)	2.0 (1, 19)
>7 days duration	13 (0.8%)	4 (0.6%)
Swelling, n (%)	178 (5.3%)	53 (1.6%)
Median time to onset (min, max)	2.0 (1, 8)	1.0 (1, 8)
Median duration (min, max)	3.0 (1, 14)	1.0 (1, 19)
>7 days duration	9 (0.5%)	2 (0.3%)

Source: Sponsor Table TSFAESOLLOC25
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Systemic Adverse Reactions

Solicited systemic ARs were reported at higher rates in vaccine than placebo recipients. The proportions of participants reporting any systemic ARs were 55.1% in the vaccine group and 35.1% in the placebo group. The proportions reporting at least one grade 3 systemic AR were

1.8% in the vaccine group and 0.6% in the placebo group. There were no reports of grade 4 systemic reactions in either group.

The most frequently reported systemic ARs were headache (vaccine versus placebo: 38.9% versus 23.7%) and fatigue (38.2% versus 21.5%). Rates of other systemic ARs in the vaccine versus placebo groups were as follows: myalgia (33.2% versus 12.7%); nausea (14.2% versus 9.7%); and fever (9.0% versus 0.6%).

Grade 3 systemic ARs were reported infrequently. The most frequently reported grade 3 systemic ARs were fatigue and myalgia, reported in 1.0% vs 0.3% and 1.0% vs. 0.2% of vaccine recipients and placebo recipients, respectively. Grade 3 fever (102.1-104°F) was reported in 0.2% of vaccine recipients and no placebo recipients.

Among participants in the vaccine group, all systemic ARs were reported more frequently among younger (18-59 years) than older (≥60 years) participants, although nausea was reported at more similar rates: 15.5% in participants 18-59 years and 12.3% in participants ≥60 years. Among vaccine group participants, rates of other systemic ARs by age group were as follows (18-59 and ≥60 years): headache (44.4% and 30.4); fatigue (43.8% and 29.7%); myalgia (39.1% and 24.0%); fever (12.8% and 3.1%).

A higher percentage of participants in the vaccine group used antipyretics/analgesics in the 7 days following vaccination compared to participants the placebo group; 19.9% versus 5.7%. This was primarily driven by participants 18-59 years old. Among participants in the vaccine group, 26.4% of those 18-59 years used antipyretics/analgesics compared to 9.8% of those ≥60 years old.

The overall rate of systemic ARs was similar in vaccine recipients who were seronegative for SARS-CoV-2 at baseline (n=3,202) and those who were seropositive at baseline (n=154): 55.4% versus 50.0%. Rates for systemic ARs by baseline serostatus were as follows (seronegative vs. seropositive): headache 38.9% vs. 38.3%; fatigue 38.3% vs. 37.0%; myalgia 33.2% vs. 32.5%; nausea 14.3% vs. 12.3%; fever 9.1% vs. 6.5%.

The table below provides rates of systemic ARs by treatment group and age group.

Table 26. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Vaccination, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S 18-59 Years N=2036 n/N (%)	Placebo 18-59 Years N=2049 n/N (%)	Ad26.COV2.S ≥60 Years N=1320 n/N (%)	Placebo ≥60 Years N=1331 n/N (%)
Any Systemic	1252 (61.5%)	745 (36.4%)	598 (45.3%)	440 (33.1%)
Grade 3	47 (2.3%)	12 (0.6%)	14 (1.1%)	9 (0.7%)
Fatigue[b]	891 (43.8%)	451 (22.0%)	392 (29.7%)	277 (20.8%)
Grade 3	25 (1.2%)	4 (0.2%)	10 (0.8%)	5 (0.4%)
Headache[b]	905 (44.4%)	508 (24.8%)	401 (30.4%)	294 (22.1%)
Grade 3	18 (0.9%)	5 (0.2%)	5 (0.4%)	4 (0.3%)
Myalgia[b]	796 (39.1%)	248 (12.1%)	317 (24.0%)	182 (13.7%)
Grade 3	29 (1.4%)	1 (<0.1%)	3 (0.2%)	5 (0.4%)
Nausea[c]	315 (15.5%)	183 (8.9%)	162 (12.3%)	144 (10.8%)
Grade 3	3 (0.1%)	3 (0.1%)	3 (0.2%)	3 (0.2%)

Adverse Reaction	Ad26.COV2.S 18-59 Years N=2036 n/N (%)	Placebo 18-59 Years N=2049 n/N (%)	Ad26.COV2.S ≥60 Years N=1320 n/N (%)	Placebo ≥60 Years N=1331 n/N (%)
Fever[d]	261 (12.8%)	14 (0.7%)	41 (3.1%)	6 (0.5%)
Grade 3	7 (0.3%)	0	1 (0.1%)	0
Antipyretic/Analgesic Use	538 (26.4%)	123 (6.0%)	130 (9.8%)	68 (5.1%)

Source: Sponsor table TSFAESOLSYS27
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
[b] Fatigue, Headache, Myalgia – Grade 3: incapacitating; prevents daily activity; use of Rx pain reliever. Grade 4: Requires E.R. visit or hospitalization
[c] Nausea –Grade 3: incapacitating; prevents daily activity. Grade 4: Requires E.R. visit or hospitalization
[d] Fever - Grade 3: ≥39.0 to ≤40.0°C or ≥102.1 to ≤104.0° F; Grade 4: >40.0°C or >104.0°F
Note: No grade 4 solicited local adverse reactions were reported.

Among participants in the vaccine group, the median time to onset of all solicited systemic ARs was within 2 days of vaccination. Median durations of systemic reactions in vaccine group participants were as follows: 2 days for fatigue, headache, and myalgia and 1 day for nausea and fever. Systemic reactions with a duration longer than 7 days were reported in vaccinated participants for all systemic ARs with the exception of fever. Percentages of vaccine group participants reporting systemic ARs with duration longer than 7 days were as follows: fatigue 1.6%, myalgia 1.1%, headache 0.7%, nausea 0.3%.

The table below provides time to onset and duration of systemic ARs by treatment group.

Table 27. Time (Days) to Onset and Duration of Solicited Adverse Events, Safety Subset[a], Study 3001

Adverse Reaction	Ad26.COV2.S N=3356	Placebo N=3380
Fatigue, n (%)	1283 (38.2%)	728 (21.5%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 113)	2.0 (1, 110)
>7 days duration	29 (1.6%)	25 (2.1%)
Headache, n (%)	1306 (38.9%)	802 (23.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 68)	1.0 (1, 62)
>7 days duration	13 (0.7%)	8 (0.7%)
Myalgia, n (%)	1113 (33.2%)	430 (12.7%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 8)
Median duration (min, max)	2.0 (1, 32)	2.0 (1, 44)
>7 days duration	20 (1.1%)	15 (1.3%)
Nausea, n (%)	477 (14.2%)	327 (9.7%)
Median time to onset (min, max)	2.0 (1, 8)	3.0 (1, 8)
Median duration (min, max)	1.0 (1, 15)	1.0 (1, 8)
>7 days duration	5 (0.3%)	4 (0.3%)
Fever, n (%)	302 (9.0%)	20 (0.6%)
Median time to onset (min, max)	2.0 (1, 8)	2.0 (1, 5)
Median duration (min, max)	1.0 (1, 7)	1.0 (1, 3)
>7 days duration	0	0

Source: Sponsor Table TSFAESOLSYS25
[a] Safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = number of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Unsolicited AEs

Through the January 22, 2021 data cutoff, 54.6% of participants in the FAS (N=43,783) had at least 2 months of follow-up. The median duration of follow-up post-vaccination for all participants was 58 days. In the safety subset (N=6,736), 99.9% of participants completed the study through Day 28. The following unsolicited AEs were specified in the protocol:

- Unsolicited AEs during the 28 days following vaccination in the safety subset
- MAAEs during the 6 months following vaccination in the FAS
- SAEs for the duration of the study in the FAS
- AEs leading to discontinuation from study participation in the FAS

Additional unsolicited AEs collected from the spontaneous reports were also analyzed in the FAS. Determination of severity for all unsolicited AE were made by investigator assessment based on definitions of severity as grades 1 through 4 (mild to potentially life threatening). Causal relationship to study vaccine was determined by study investigator and classified as "related" or "not related."

AEs associated with molecularly confirmed SARS-CoV-2 infection were not included in the analysis of AEs.

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs in the safety subset that occurred within 28 days of vaccination and at rates of ≥1% in the vaccine group. The proportions of participants with unsolicited AE were 13.1% and 12.0% in the vaccine and placebo groups, respectively. Overall, rates of unsolicited adverse events, including events grade 3 or higher, were similar between the treatment groups.

Table 28. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Safety Subset[a], Study 3001

System Organ Class Preferred Term	Ad26.COV2.S N=3356 Any Grade n (%)	Ad26.COV2.S N=3356 ≥Grade 3 n (%)	Placebo N=3380 Any Grade n (%)	Placebo N=3380 ≥Grade 3 n (%)
General disorders and administration site	211 (6.3%)	5 (0.1%)	134 (4.0%)	2 (0.1%)
Chills	67 (2.0%)	1 (<0.1%)	19 (0.6%)	0
Fatigue	64 (1.9%)	1 (<0.1%)	77 (2.3%)	1 (<0.1%)
Vaccination site pain	42 (1.3%)	1 (<0.1%)	22 (0.7%)	0
Musculoskeletal and connective tissue disorders	103 (3.1%)	3 (0.1%)	89 (2.6%)	4 (0.1%)
Myalgia	49 (1.5%)	0	58 (1.7%)	2 (0.1%)
Arthralgia	35 (1.0%)	1 (<0.1%)	24 (0.7%)	2 (0.1%)
Nervous system disorders	98 (2.9%)	3 (0.1%)	108 (3.2%)	5 (0.1%)
Headache	72 (2.1%)	1 (<0.1%)	82 (2.4%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	93 (2.8%)	3 (0.1%)	88 (2.6%)	4 (0.1%)
Nasal congestion	40 (1.2%)	1 (<0.1%)	38 (1.1%)	2 (0.1%)
Cough	33 (1.0%)	1 (<0.1%)	33 (1.0%)	0

System Organ Class Preferred Term	Ad26.COV2.S N=3356 Any Grade n (%)	Ad26.COV2.S N=3356 ≥Grade 3 n (%)	Placebo N=3380 Any Grade n (%)	Placebo N=3380 ≥Grade 3 n (%)
Gastrointestinal disorders	87 (2.6%)	2 (0.1%)	90 (2.7%)	2 (0.1%)
Diarrhea	33 (1.0%)	2 (0.1%)	35 (1.0%)	0
Infections and infestations	57 (1.7%)	3 (0.1%)	87 (2.6%)	6 (0.2%)

Source: Sponsor Tables TSFAEUNSOL02_D & TSFAEUNSOL03_D
[a] safety subset: Subset of Full-Analysis Set for analysis of solicited and unsolicited AEs
n = # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.2% of vaccine recipients and 4.6% of placebo recipients. The proportions of participants who reported grade 3 or higher unsolicited AEs were 0.6% following vaccine (19 participants) and 0.5% following placebo (18 participants).

Unsolicited Adverse Events of Clinical Interest

FDA conducted both broad and narrow Standardized MedDRA Queries (SMQs) using FDA-developed software to evaluate unsolicited adverse events of clinical interest by searching preferred terms (PTs) that could together represent various conditions, including but not limited to allergic, neurologic, inflammatory, vascular, and autoimmune disorders. Narrow searches were done to identify cases highly likely to be the condition of interest whereas broad searches were done to identify all possible cases. Ten SMQs (broad and narrow combined) were conducted on AEs reported through the data cutoff date (requiring 2 months median follow-up following vaccination) and included events that occurred in the FAS (N=43,783). AEs in the FAS were collected through protocol specified collection methods as well as spontaneous reporting by study participants.

SMQs and associated PTs for which adverse events were reported at higher rates in vaccine recipients compared to placebo recipients are discussed below. For the additional SMQs, rates were comparable between vaccine and placebo recipients.

The SMQ for “embolic and thrombotic events” in the FAS demonstrated a slight numerical imbalance; data through the cutoff date includes reports of such events among 0.06% of vaccine recipients (15 events in 14 participants) compared to 0.05% of placebo recipients (10 events in 10 participants). By PT, deep vein thrombosis (including PTs for “deep vein thrombosis,” “venous thrombosis limb” and “embolism venous”) was reported in 6 vaccine recipients (5 events within 28 days of vaccination) and 2 placebo recipients (2 events within 28 days of vaccination). Pulmonary embolism was reported in 4 vaccine recipients (2 events within 28 days of vaccination) and 1 placebo recipient (1 event within 28 days of vaccination). Cerebrovascular events (including PTs “cerebral infarction”, “transverse sinus thrombosis”, “hemiparesis”, “cerebrovascular accident”, “carotid artery occlusion” and “ischemic stroke”) were reported in 3 vaccine recipients (4 events, 3 events within 28 days of vaccination) and 3 placebo recipients (3 events within 28 days of vaccination). Myocardial infarction was reported in 1 vaccine recipient (1 event within 28 days of vaccination) and 3 placebo recipients (2 events within 28 days of vaccination). One placebo recipient reported thrombosed hemorrhoids within 28 days of vaccination. Table 29 summarizes thromboembolic events in both vaccine and placebo recipients including investigator assessment of grade, seriousness and causality.

Table 29. Thromboembolic Events in Vaccine and Placebo Recipients, Full Analysis Set, Study 3001

Investigational Product	Adverse Event (PT)	Age/Sex	Day of Onset	Resolution Status	Grade/SAE[a]	Related[a]
Ad26.COV2.S	Deep vein thrombosis	90/M	13	Resolving	2/N	No
Ad26.COV2.S	Deep vein thrombosis	42/M	19	Unresolved	2/N	No
Ad26.COV2.S	Deep vein thrombosis	63/M	22	Resolved	4/Y	No
Ad26.COV2.S	Venous thrombosis limb	63/M	23	Resolved	2/N	No
Ad26.COV2.S	Deep vein thrombosis	52/M	27	Resolving	2/N	Yes
Ad26.COV2.S	Embolism venous	72/M	36	Unresolved	2/Y	No
Ad26.COV2.S	Pulmonary embolism	30/F	3	Resolved	4/Y	No
Ad26.COV2.S	Pulmonary embolism	68/M	7[c]	Unresolved	2/N	No
Ad26.COV2.S	Pulmonary embolism	54/M	45	Resolved	3/Y	No
Ad26.COV2.S	Pulmonary embolism	66/M	57	Unresolved	3/Y	No
Ad26.COV2.S	Transverse sinus thrombosis	25/M	21	Resolved	4/Y	No
Ad26.COV2.S	Cerebral infarction[b]	82/M	23	Resolving	4/Y	No
Ad26.COV2.S	Hemiparesis	49/F	28	Unresolved	1/Y	No
Ad26.COV2.S	Ischemic stroke[b]	82/M	41	Resolving	4/Y	No
Ad26.COV2.S	Myocardial infarction	70/M	12	Resolved	3/Y	No
Placebo	Deep vein thrombosis	57/M	3	Unresolved	2/N	No
Placebo	Deep vein thrombosis	44/M	6	Resolving	4/Y	Yes
Placebo	Pulmonary embolism	53/M	29	Resolving	4/Y	No
Placebo	Carotid artery occlusion	58/F	9	Resolving	4/Y	No
Placebo	Hemiparesis	45/M	9	Resolving	2/N	No
Placebo	Cerebrovascular accident	71/F	22	Unresolved	3/Y	No
Placebo	Acute myocardial infarction	78/M	3	Resolved	3/Y	No
Placebo	Acute myocardial infarction	52/F	4	Resolved with sequelae	4/Y	No
Placebo	Acute myocardial infarction	61/M	62	Fatal	4/Y	No
Placebo	Hemorrhoids thrombosed	42/F	24	Resolved	1/N	No

[a] Classification of events as SAEs and relatedness determined by study investigators
[b] Events occurred in the same study participant
[c] This event was initially reported with day of onset of 20 days. Day updated based on Sponsor clarification obtained on 2/17/21.

Additional details are provided for selected events among vaccine recipients for which a contributory effect of the vaccine could not be excluded based on FDA assessment of the clinical information provided:

- A 25-year-old male with no past medical history and no concurrent medications experienced a transverse sinus thrombosis on Day 21 following vaccination. On Day 9 the participant experienced symptoms of fever, myalgia, headache, fatigue, abdominal pain, congestion and rhinorrhea. He tested negative for SARs-CoV-2 during this acute illness. Aside from headache, his symptoms improved. On Day 19 he experienced a tonic-clonic seizure. A CT scan without contrast demonstrated a cerebral hemorrhage. On Day 21, a transverse sinus thrombosis was reported on a venogram. The participant underwent a thrombectomy as well as stent placement for stenosed right sigmoid sinus on Day 22. On Day 23 repeat venogram showed the presence of a new clot in the transverse sinus. A second thrombectomy with venoplasty was performed. Treating clinicians reported observing rapid thrombus formation during the two thrombectomy procedures that was consistent with a clinically hypercoagulable state. In their assessment, the transverse sinus thrombosis most likely occurred days before the participant's clinical presentation with a seizure; the seizure was reported to be a consequence of a secondary bleed caused by elevated venous pressure from the venous flow obstruction. Workup for hematologic and infectious causes of the thrombosis did not reveal an etiology. This event was initially thought to be related to the study product by the investigator and prompted a study pause. After thorough investigation and expert consultation no clear cause of the event was identified; however possible contributing factors, such as preceding infection and an anatomical anomaly, were suggested. The investigator's brochure and informed consent form were updated accordingly, and the study pause was lifted. The investigator and Sponsor's final assessment of this event was that it was not related to the study product.

- A 30-year-old female with hypothyroidism, obesity (body mass index: 36.5 kg/m^2), headaches, anxiety and depression and use of multiple medications including medroxyprogesterone, experienced a pulmonary embolism on Day 3 following vaccination. The participant was hospitalized following a syncopal episode and CT scan of the chest demonstrated an occlusive thrombus in a pulmonary artery. Treating clinicians attributed the pulmonary embolism to hypercoagulability due to medroxyprogesterone acetate birth control. The event was not considered related to the study product by the investigator or the Sponsor. The last date of medroxyprogesterone acetate is not recorded.

- A 52-year-old male with obesity (body mass index: 32.4 kg/m^2) experienced a deep vein thrombosis (DVT) on Day 27 following vaccination. The participant experienced calf pain following physical activity on Day 13. An ultrasound on Day 27 demonstrated a DVT in a vein of the left calf. The event was considered non-serious by the investigator and related to the study product. The Sponsor considered the event not related to the study product.

- A 63-year-old male with type 2 diabetes, hypertension and osteoarthritis experienced a DVT on Day 23 following vaccination. The event was considered non-serious and not related to the study product by the investigator.

- A 49-year-old female with no past medical history and medication use including medroxyprogesterone experienced hemiparesis on Day 28 following vaccination. The event was considered serious by the investigator. No laboratory or imaging results were reported.

The event was unresolved and ongoing on Day 51. The event was not considered related to the study product by the investigator or the Sponsor.

Assessment of the cases above is confounded by the presence of risk factors in the individual participants. Nevertheless, given the numerical imbalance between vaccine and placebo recipients and temporal relationship, vaccine cannot be excluded as a contributing factor. As such, data at this time are insufficient to determine if there a causal relationship between the vaccine and thromboembolic events. FDA will recommend surveillance for further evaluation of thromboembolic events with deployment of the vaccine into larger populations.

The SMQ for "convulsions" in the FAS demonstrated a numerical imbalance, with single events in 4 vaccine recipients and 1 event in a placebo recipient. All of the convulsion events reported by the vaccine recipients occurred within 28 days of vaccination. Two events in the vaccine groups were considered serious. Of the two serious events, one event was discussed above and occurred secondary to a cerebral hemorrhage in a participant with a transverse sinus thrombosis. The other serious event and one of the non-serious events occurred in participants with a history of seizures. FDA's assessment is that these events are unlikely related to the study vaccine.

The SMQ for "hearing and vestibular disorders" included the PT "tinnitus" for which was a numerical imbalance was observed across treatment groups. Tinnitus was reported in 6 vaccine recipients (6 events) compared to no placebo recipients. Events of tinnitus are summarized in the table below.

Table 30. Tinnitus in Vaccine Recipients, Full Analysis Set, Study 3001

Investigational Product	Age/Sex	Day of Onset	Resolution Status	Grade/ SAE[a]	Possible Risk Factor(s)	Related[a]
Ad26.COV2.S	58/M	1	Resolving	1/N	Hypertension	No
Ad26.COV2.S	63/F	1	Resolved	1/N	Hypothyroidism	Yes
Ad26.COV2.S	25/F	2	Resolved	1/N	Allergic rhinitis, medication use	Yes
Ad26.COV2.S	51/M	12	Unresolved	1/N	Hypertension, hypothyroidism, medication use	No
Ad26.COV2.S	54/M	17	Resolving	1/N	Allergic rhinitis	No
Ad26.COV2.S	65/F	22	Resolving	2/N	History of tinnitus	No

[a] Classification of events as SAEs and relatedness determined by study investigators

An additional event of tinnitus was reported in the clinical development of Ad26.COV2.S. The event, reported in Study 1002, occurred in 21-year-old male with no reported past medical history and no concomitant medications who experienced sudden hearing loss on Day 34 post-vaccination with Ad26.COV2.S. The hearing loss was associated with tinnitus and blocked ear sensation. Testing revealed sensorineural hearing loss. Workup for etiology including laboratory tests and imaging did not reveal an etiology. Hearing improved and the event was resolved by Day 69. The event was not considered related to the study product by the investigator or the Sponsor.

Assessment of these cases is confounded by the presence of risk factors in the individual participants. As such, data at this time are insufficient to determine if there a causal relationship between the vaccine and tinnitus.

The SMQ for “angioedema” in the FAS demonstrated a numerical imbalance, with events reported among 0.2% of vaccine recipients (44 events in 44 participants) compared to 0.12% of placebo recipients (28 events in 27 participants). By PT, “urticaria” was reported in 8 vaccine recipients compared to 3 placebo recipients. Within 7 days of vaccination, 5 events occurred in the vaccine group and 1 event occurred in the placebo group, all of which were grade 1 or 2. Based on temporal association and biologic plausibility, FDA’s assessment is that the events of urticaria are possibly related to study vaccine.

The PT “wheezing” was reported in 12 vaccine recipients (0.05%) and 7 placebo recipients (0.03%). However, there was no meaningful imbalance in events within 7 days of vaccination, with 4 events occurring each group; one event in the placebo group was grade 3 and all others were grade 1 or 2.

The SMQ for “arthritis” in the FAS demonstrated a numerical imbalance, with events reported among 0.5% of vaccine recipients (110 events in 109 participants) compared to 0.36% of placebo recipients (83 events in 78 participants). By PT, “arthralgia” was reported in 91 vaccine recipients (92 events) compared to 62 placebo recipients (67 events). In vaccine recipients, 56 of these events (60.8%) occurred within 7 days following vaccination compared to 24 events (35.8%) in placebo recipients. FDA’s assessment is that these events likely represent vaccine reactogenicity.

The SMQ for “peripheral neuropathy” in the FAS demonstrated a numerical imbalance, with events reported among 0.21% of vaccine recipients (47 events in 45 participants) compared to 0.16% of placebo recipients (36 events in 35 participants). By PT, “muscular weakness” was reported by 31 vaccine recipients compared to 18 placebo recipients. In vaccine recipients, 18 of these events (58.1%) occurred within 7 days following vaccination compared to 6 events (33.3%) in placebo recipients. FDA’s assessment is that these events likely represent vaccine reactogenicity.

Immediate Adverse Events

Immediate unsolicited reactions occurring within 30 minutes of vaccination were infrequent and occurred in 0.2% of participants in both the vaccine and placebo groups. There were no reports of anaphylaxis immediately following vaccination.

Serious Adverse Events

Deaths

As of January 22, 2021, 19 deaths were reported (3 vaccine, 16 placebo). Two deaths in the vaccine group were secondary to respiratory infections not due to COVID-19. A 61-year-old participant died of pneumonia on Day 24 following onset of symptoms on Day 13. A 42-year-old participant with HIV died on Day 59 following diagnosis of a lung abscess on Day 33. A 66-year-old participant died of unknown causes after waking up with shortness of breath on Day 45. The placebo recipients died of pneumonia (n=2), suicide (n=1), accidental overdose (n=1), myocardial infarction (n=1), malaise (n=1), unknown cause (n=3) and confirmed COVID-19 (n=6). An update on deaths reported from the time period of January 22 to February 5 included an additional 6 deaths. Of these 6 deaths, 2 occurred in the vaccine group and 4, including 1 due to COVID-19, occurred in the placebo group. None were related to the study product.

Non-fatal Serious Adverse Events

The proportions of participants who had at least one SAE reported through January 22, 2021 were 0.4% in the vaccine group and 0.4% in the placebo group. The most commonly reported SAE was appendicitis occurring in 6 vaccine recipients and 5 placebo recipients. There were no significant numerical imbalances in SAEs by preferred term.

Seven SAEs occurring in 7 vaccine recipients and 3 SAEs occurring in 2 placebo recipients were assessed by the investigator as related to study vaccination (Table 31). Of the 7 SAEs in the vaccine group, the Sponsor assessed 3 as related/likely related, 2 as possibly related, 2 as unrelated to the vaccine.

Table 31. SAEs Considered Related by Investigator, Full Analysis Set, Study 3001

Investigational Product	SAE (PT)	Age/Sex	Day of Onset	Resolution Status	Grade	Related (Sponsor Assessment)
Ad26.COV2.S	Radiculitis brachial	30/M	1	Unresolved	3	Yes (Reassessed as injection site pain)
Ad26.COV2.S	Post-vaccination syndrome	35/M	2	Resolved	3	Yes (Reassessed as reactogenicity)
Ad26.COV2.S	Facial paralysis	62/M	3	Resolving	2	No
Ad26.COV2.S	Vaccination site hypersensitivity	42/M	3	Resolved	3	Likely
Ad26.COV2.S	Facial paralysis	43/M	16	Resolving	2	No
Ad26.COV2.S	Guillain-Barre Syndrome	60/F	16	Unresolved	4	Possibly
Ad26.COV2.S	Pericarditis	68/M	17	Resolved	4	Possibly
Placebo	Deep vein thrombosis	44/M	6	Resolving	4	Indeterminate
Placebo	Epstein-Barr infection[a]	69/M	14	Resolved	3	No
Placebo	Atrial flutter[a]	69/M	21	Resolving	3	No

[a] Events occurred the same study participant

In FDA's opinion following review of narratives, the following 3 SAEs in the vaccine group are considered likely related to the study vaccine:

- A 42-year-old male with no personal or family history of allergic reactions experienced diffuse urticaria beginning on Day 3 following vaccination accompanied with systemic symptoms of fatigue, myalgia and arthralgia. Over the following two days the urticaria progressed, and the participant experienced angioedema of the lips as well as the sensation of itchy and tight throat, but no hypoxia or respiratory distress. The event did not meet Brighton Criteria for anaphylaxis. FDA's assessment is that this event was likely a hypersensitivity reaction to the study vaccine.

- A 30-year-old male was reported to have "brachial neuritis following vaccination" (PT: "radiculitis brachial") with pain at the site of vaccine administration on Day 1 which persisted and worsened over several days and was unresponsive to non-prescription analgesics. Evaluation included electroconductive studies, which revealed intact nerves with no denervation of the evaluated muscles, and MRI of the cervical spine, which did not reveal an etiology of the participant's symptoms. FDA's assessment of this event is that the pain at injection site is likely related to the vaccine, however the diagnosis of brachial neuritis is unlikely given the findings on electroconductive studies.

- A 35-year-old male experienced generalized malaise, weakness, myalgia, shortness of breath, headache, sensation of numbness and tingling in upper extremities, chest pain and fever beginning on Day 2 following vaccination. The participant was hospitalized for exacerbated generalized weakness. Abnormal vital signs included fever (39.4°C), blood pressure (129/103 mmHg), heart rate (112bpm) and respiratory rate (19 breaths per minute). There was no hypoxia. On exam he complained of diffuse tenderness in the extremities. No abnormalities were noted on neurologic exam which included normal reflexes. Abnormal laboratory findings included a mild elevation of creatine kinase attributed to mild myositis. Laboratory testing was negative for COVID-19, influenza and RSV. Symptoms resolved by Day 4. FDA's assessment of this event is that it is likely systemic reactogenicity related to the study vaccine.

For the SAE of pericarditis, as no alternative etiology was determined, FDA's assessment is that the possibility that the vaccine contributed to the event cannot be excluded. Review of Janssen's safety database including all Ad26-based vaccines did not reveal any additional reports of pericarditis.

Reports of facial paralysis (Bell's Palsy) were overall balanced between vaccine and placebo recipients (2 vaccine, 2 placebo). In addition to the 2 SAEs of facial paralysis presented in Table 31 above, a third event in a 54-year-old vaccine recipient occurred on Day 19, described as facial swelling and "droopiness" with no facial asymmetry and intact cranial nerves II-XII. This event was not considered related by the investigator. In FDA's assessment, description of this event is not consistent with facial paralysis. Two events of facial paralysis were reported in placebo recipients on Days 2 and 29.

There were single reports of Guillain-Barre Syndrome (GBS) in a 60-year-old vaccine recipient and a 75-year-old placebo recipient occurring on Days 16 and 10, respectively. The event in the vaccine group was preceded by symptoms of chills, nausea, diarrhea and myalgia. In FDA's assessment the events of facial paralysis and GBS are unlikely related to study vaccine but a causal relationship cannot be definitively excluded.

During FDA's review of the EUA request, the Sponsor reported an SAE of anaphylaxis following vaccination with Ad26.COV2.S in an ongoing, open-label study in South Africa. The Sponsor reported that based on available information, the SAE met the Brighton Collaboration case definition for anaphylaxis with level 2 diagnostic certainty, although the event remains under investigation with additional details being collected.

Subgroup Analyses

With the exception of more frequent, generally mild to moderate reactogenicity in participants 18-59 years of age, there were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to vaccination. Participants were excluded if they were pregnant or planned to become pregnant within 3 months of vaccine administration. The study is collecting outcomes for all reported pregnancies in study participants.

Eight pregnancies were reported through January 22, 2021 (4 vaccine, 4 placebo). In 7 participants (3 vaccine, 4 placebo) vaccination was within 30 days after last menstrual period (LMP) and in 1 vaccine recipient vaccination was prior to LMP. Unsolicited AEs related to pregnancy include spontaneous abortion (1 vaccine, 0 placebo), incomplete abortion (0 vaccine, 1 placebo), elective abortion (0 vaccine, 2 placebo) and ectopic pregnancy (1 vaccine, 0 placebo). Among participants in the vaccine group, two pregnancies are ongoing with outcomes unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in rabbits was submitted to FDA on January 19, 2021. FDA review of this study concluded that Ad26.COV.S given prior to mating and during gestation periods at dose of $1x10^{11}$ vp (2 times the human dose) did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal development.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the Ad26.COV2.S vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=43,783; 21,895 vaccine, 21,888 placebo) meets the expectations for efficacy in FDA's guidance for industry Development and Licensure of Vaccines to Prevent COVID-19 (June 2020). A subset of participants (N=6,736) was followed for solicited reactions within 7 days following vaccination and unsolicited reactions within 28 days following vaccination. The demographic and baseline characteristics of the all-enrolled population and the safety subset were similar with respect to age and sex but had imbalances with respect to race, baseline comorbidities, SARS-CoV-2 serostatus and geographic distribution.

Local site reactions and systemic solicited events among vaccine recipients were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (48.6%), headache (38.9%), fatigue (38.2%) and myalgia (33.2%); 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, were reported as grade 3. Overall, solicited reactions were reported more commonly in younger participants.

There were no meaningful imbalances in unsolicited adverse events in 28 days following vaccination between vaccine and placebo recipients in the safety subset. Among all adverse events collected through the data cutoff of January 22, 2021, a numerical imbalance was seen in urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days of vaccination which is possibly related to the vaccine. Numerical imbalances were reported between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0). Based on currently available information, a contributory effect of the vaccine could not be excluded, although the imbalance was small (representing a difference of 0.06% of vaccine recipients vs. 0.05% of placebo recipients), and many of the participants had predisposing conditions. FDA will recommend surveillance for further evaluation of thromboembolic events with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events that would suggest a causal relationship to Ad26.COV2.S.

As of February 5, 2021, a total of 25 deaths were reported in the study (5 vaccine, 20 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups and include 7 deaths in the placebo group due to COVID-19 infection. Non-fatal serious adverse events, excluding those due to COVID-19, were infrequent and balanced

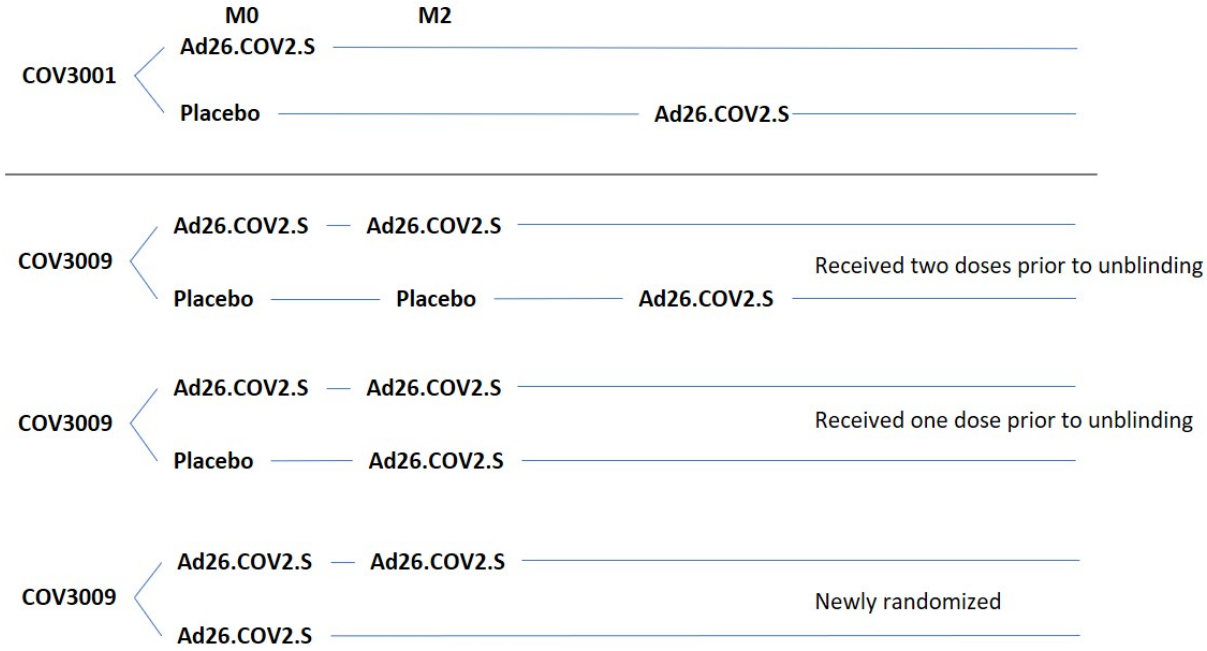
between treatment groups with respect to rates and types of events (0.4% in both groups). A serious event of a hypersensitivity reaction, not classified as anaphylaxis, beginning 2 days following vaccination was likely related to receipt of the vaccine. A single event of anaphylaxis following vaccination with Ad26.COV2.S, the details of which are still under investigation, was reported by the Sponsor to have occurred in an ongoing open-label study in South Africa.

5. FDA Review of Other Information Submitted in Support of the EUA

5.1 Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-up

In the event that the Ad26.COV2.S vaccine receives FDA authorization for emergency use, the Sponsor proposes to submit a protocol amendment to Study 3001 that would allow all participants who received placebo to receive the vaccine (Figure 2). This would effectively result in unblinding of participants and investigators. However, participants who crossover from placebo will be encouraged to remain in the study up to 2 years after vaccination so that they may be followed for efficacy/effectiveness, safety, and immunogenicity. The Sponsor anticipates that open-label crossover vaccination would also be offered to placebo recipients in the ongoing Phase 1 and 2 studies. Janssen also proposes offering a single dose of Ad26.COV2.S to enrolled participants who initially received two doses of placebo in study COV3009. Because the study is expected to still be enrolling, participants who received a first dose of placebo will receive a dose of Ad26.COV2.S as their second dose and participants yet to be enrolled will be randomized to either a single-dose or a two-dose schedule of Ad26.COV2.S. Crossover vaccination would be made available to U.S. participants as soon as operationally feasible following the issuance of an EUA. Study investigators will be encouraged to consider current local public health guidance for determining the scheduling priority of participants.

Figure 2. Sponsor's Proposed Crossover Design Following Issuance of an EUA



5.2 Pharmacovigilance Activities

Janssen submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with the Janssen COVID-19 vaccine. The Sponsor identified vaccine-associated enhanced disease (including vaccine-associated enhanced respiratory disease), anaphylactic reactions (including anaphylaxis), and thromboembolic events as Important Potential Risks.

Important Missing Information includes: use during pregnancy and lactation, use in immunocompromised patients, use in patients with autoimmune or inflammatory disorders, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, and cardiovascular disorders), interaction with other vaccines, long-term safety, and use in pediatrics.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Serious adverse events (regardless of attribution to vaccination)
- Multisystem inflammatory syndrome
- COVID-19 disease resulting in hospitalization or death

The Sponsor will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- A narrative summary and analysis of vaccine administration errors whether or not associated with an adverse event, that were identified since the last reporting interval
- Safety concerns newly identified in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to fact sheets given to vaccination providers, changes made to studies, or studies initiated)

The Sponsor plans to conduct long-term follow-up of participants in the ongoing clinical trials. The Sponsor has also submitted protocols for the post-authorization studies listed below. FDA is reviewing the protocols and will provide feedback.

Pregnancy study: multi-country, observational, prospective cohort study of pregnant women vaccinated with Ad26.COV2.S to assess obstetric, neonatal, and infant outcomes

Active surveillance study of safety: retrospective, observational, propensity-scored matched cohort study using health insurance claims and electronic health records to assess the risk of prespecified adverse events of special interest following vaccination with Ad26.COV2.S

Active surveillance study of effectiveness: retrospective, observational propensity-scored matched cohort study using health insurance claims and electronic health records to estimate the effectiveness of Ad26.COV2.S to prevent medically attended COVID-19 in individuals vaccinated according to national immunization recommendations

Reporting to VAERS and Janssen

Providers administering the Ad26.COV2.S vaccine must report to VAERS and, to the extent feasible, report to Janssen the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (regardless of attribution to vaccination)
- Multisystem inflammatory syndrome
- COVID-19 disease resulting in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe, a smartphone-based opt-in program that uses text messaging and web surveys to help COVID-19 vaccine recipients monitor for and report side effects. The system also will provide telephone follow-up to anyone who reports medically important adverse events. Responses indicating missed work, inability to do normal daily activities, or receipt of care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

5.3 Non-Clinical Studies

Toxicology Studies

To support their EUA request, Janssen submitted the following toxicology studies:

(1) Repeat-dose toxicity study of Ad26.COV2.S by repeated intramuscular administration to New Zealand White rabbits, Study# TOX14382, reviewed under IND 22657.

(2) Intramuscular combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in New Zealand White rabbit, Study# TOX14389, reviewed under IND 22657.

Based on the nonclinical toxicity assessment, there were no significant safety issues to report. Three intramuscular injections of Ad26.COV2.S at a dose of $1x10^{11}$ vp were well tolerated in rabbits. Intramuscular administrations of Ad26.COV2.S at a dose of $1x10^{11}$ vp to rabbits prior to mating and during the gestation period did not reveal adverse effects on female reproduction, fetal/embryonic development and postnatal development.

Other Non-Clinical Studies

Several nonclinical studies in mice, rabbits, Syrian hamsters, and non-human primates (NHP) (rhesus monkeys, Macaca mulatta) were conducted to support the safety and efficacy of Ad26.COV2.S. The vaccine was assessed for immunogenicity and for protection against SARS-CoV-2 following challenge with wild-type virus. Ad26.COV2.S elicited SARS-CoV-2 neutralizing and S protein binding antibodies in all species following intramuscular inoculation. Immunization with Ad26.COV2.S consistently induced IFN-γ production in mice, rabbits, and NHP and elicited a Th1 skewed immune response in mice and NHP. In a SARS-CoV-2 Syrian hamster challenge model, Ad26.COV2.S significantly reduced viral load in the lung compared with mock vaccinated controls. In all Syrian hamsters vaccinated with Ad26.COV2.S, including animals showing breakthrough infection in the lung, no increased lung histopathology, infectious viral load, or body weight loss was observed compared with the control group, indicating the absence of any signs of Vaccine-Associated Enhanced Respiratory Disease (VAERD). In an NHP challenge model, immunization with Ad26.COV2.S resulted in reduced lung and nasal swab

viral load. No clinical or histopathologic evidence of VAERD was observed in NHP at any dose level or regimen.

Overall, the submitted non-clinical data were found to be supportive of the safety and effectiveness of Ad26.COV2.S.

5.4 Chemistry, Manufacturing, and Control (CMC) Information

The Ad26.COV2.S drug substance (DS) is manufactured in PER.C6 TetR cells. No fetal bovine serum or other materials of animal origin are used during DS manufacture. No antibiotics are used during DS manufacture. PER.C6 TetR cell banks and Ad26.COV2.S virus seeds were found to be free of detectable bacterial and mycoplasma contaminants and adventitious agents. The DS manufacturing process consists of (b) (4) stages, which include cell expansion and virus production, (b) (4) purification, formulation, filling and freezing. The Ad26.COV2.S drug product (DP) manufacturing process consists of (b) (4) stages, which include formulation buffer preparation, DS thawing, DP formulation, sterile filtration and filling, and visual inspection, labeling, packaging and storage. To support the EUA request, in-process, release, and characterization data for three process performance qualification (PPQ) DS batches for the DS manufacturing facility (Janssen Vaccines & Prevention B.V. Leiden, The Netherlands) (JVL) were provided. In-process, release, and characterization data for three PPQ DP lots from the DP manufacturing facility (Grand Rapids Aseptic Manufacturing, Inc Grand Rapids, MI USA) (GRAM) were provided. The Sponsor will submit the Certificates of Analysis (CoAs) for DS and DP batches to be used under the EUA for review at least 48 hours prior to distribution. This includes batches manufactured at the sites authorized under the initial EUA and additional sites authorized as part of future EUA amendments.

Minor changes were introduced throughout the development of the DS manufacturing process between Phase 1/2, Phase 3 and Phase 3 initial lots; the latter corresponding to the process intended for production of the EUA vaccine lots. The Sponsor performed comparability studies between the DS manufacturing process variations, S-VAL-1, S-VAL-2, S-VAL-3 and S-VAL-4. The submitted data support the comparability of DS produced from the different processes. Minor changes were made to the DP manufacturing process during vaccine development. The clinical DP batches were manufactured at 3 different manufacturing sites compared to the single site used for EUA DP manufacturing.

All available stability data generated using platform Ad26 vaccines and the Ad26.COV2.S DS and DP lots support use of the vaccine under EUA. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of Ad26.COV2.S DS and DP include tests to ensure safety, identity, purity, quality, and potency. The assays are appropriate and acceptable to be used for the control of DS and DP quality. All analytical procedures used for the release of the DS and DP have been adequately validated. The summaries of the validation results demonstrate precision, accuracy, sensitivity, specificity, and reproducibility for each evaluated analytical assay, indicating that they are suitable for the intended use.

No significant issues were identified during the EUA review of either the DS or DP CMC information.

The manufacture of the Janssen COVID-19 vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as described in the guidance, Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021, originally issued October 2020), to ensure that the manufacturers have adequate control of their manufacturing process and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.
- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms was adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also gathered information to determine and document facts at one of the facilities, reviewed the inspectional histories of all applicable facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Janssen COVID-19 vaccine under an Emergency Use Authorization.

5.5 Clinical Assay Information

Information for the Abbott RealTime reverse transcriptase (RT) polymerase chain reaction (PCR) assay for detection of SARS-CoV-2 in clinical specimens and the Roche Elecsys Anti-SARS-CoV-2 immunoassay for the evaluation of serostatus to SARS-CoV-2 was submitted to IND 22657/54 and IND 22657/119. The Abbott RT-PCR assay is performed at the University of Washington, Dept of Laboratory Medicine and the Roche Elecsys Anti-SARS-CoV-2 assay is performed by (b) (4) . Both assays were validated at the respective testing sites and found to be acceptable for the intended uses.

5.6 Inspections of Clinical Study Sites

BIMO inspections were conducted at five domestic clinical investigator sites participating in the conduct of study Protocol VAC31518COV3001, “A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older.” The inspections did not reveal problems impacting the data submitted in support of this EUA.

5.7 EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, Fact Sheet for Recipients were reviewed, and suggested revisions sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

6. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

6.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after vaccination
- Reduction in the risk of confirmed severe COVID-19 (including reduction in the risk of COVID-19 requiring medical intervention) occurring at least 14 days after vaccination

The vaccination regimen was effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the vaccine. The vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and for more severe disease, including COVID-19 requiring medical intervention, considering all cases starting 14 days after vaccination. Efficacy findings were also generally consistent across evaluable subgroups, including by age, race, ethnicity, and risk for severe COVID-19. Although VE estimates appeared to be lower in the subgroup of participants 60 years of age and older with comorbidities, an increase in VE estimates and narrowing of the CI was observed with inclusion of more cases (i.e., starting at 14 days post-vaccination and cases not yet centrally confirmed), indicating that the results seen potentially reflect imprecision associated with smaller numbers of cases. Additionally, case splits for COVID-19 requiring medical attention among participants 60 years of age and older with comorbidities further support benefit of the vaccine in this subgroup. Although a lower efficacy overall was observed in South Africa, where there was a predominance of B.1.351 lineage during the time period of this study, vaccine efficacy against severe/critical COVID-19 was similarly high across the United States, South Africa, and Brazil.

The vaccine is administered as a single dose, which provides operational benefits to mass vaccination campaigns.

6.2 Unknown Benefits/Data Gaps

Duration of protection

As the analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at higher risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the

Ad26.COV2.S vaccine for individuals with prior infection with SARS-CoV2, there were limited cases of COVID-19 among study participants with positive SARS-CoV-2 infection status at baseline. The study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of September 21, 2020 to January 22, 2021, in sites across the United States, South Africa, and 6 countries in Latin America, which was a setting of high disease incidence with several regionally circulating SARS-CoV-2 variants. The evolution of the pandemic characteristics, including potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Available Day 71 N-serology data from a small subset of participants in the study, with infrequent evaluations of serological and virological measurements, are limited to assess the effect of the vaccine in preventing asymptomatic infection. There is uncertainty about the interpretation of these data and definitive conclusions cannot be drawn at this time.

Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization and including additional data to support the sensitivity of serologic and virologic surveillance methods.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[9-12] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

6.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting 1 to 2 days. The most common solicited adverse reactions were injection site pain (48.6%), headache (38.9%), fatigue (38.2%) and myalgia (33.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, were reported as grade 3. Overall, solicited reactions were reported more commonly in younger participants. Among all adverse events collected through the data cutoff of January 22, 2021, a numerical imbalance was seen in urticaria events reported in the vaccine group (n=5) compared to placebo group (n=1) within 7 days of vaccination with is possible related to vaccination. Numerical imbalances were also observed between vaccine and placebo recipients for thromboembolic events (15 versus 10) and tinnitus (6 versus 0), with many of the participants experiencing these events having predisposing risk factors. Data at this time are insufficient to determine a causal relationship between these events and the vaccine.

Serious adverse events, while uncommon (0.4% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs that occurred in the vaccine group, FDA considered 3 as related: hypersensitivity reaction, not classified as anaphylaxis (n=1), severe and persistent injection site pain (n=1), and severe systemic reactogenicity (n=1). For the serious adverse events of pericarditis, facial paralysis and GBS, data are insufficient to determine a causal relationship to vaccination. A single event of anaphylaxis following vaccination with Ad26.COV2.S, the details of which are still under investigation, was reported by the Sponsor to have occurred in an ongoing open-label study in South Africa.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

6.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals and their infants, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of Ad26.COV2.S in female rabbits concluded that Ad26.COV2.S given prior to mating and during

gestation periods at dose of $1x10^{11}$ vp (2 times human dose) did not have any effects on female reproduction, fetal/embryonal development, or postnatal development.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial population of approximately 20,000 vaccine recipients over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

7. VRBPAC Meeting Summary

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on February 26, 2021 to discuss Janssen's EUA request. The meeting agenda included: an overview by FDA on EUA and considerations specific to COVID-19 vaccines; presentations by the CDC on the epidemiology of COVID-19 strain variants and post-marketing surveillance data from currently authorized COVID-19 vaccines; an FDA overview of plans for additional post-marketing surveillance; a public comment period; presentations of data from studies of the Janssen COVID-19 vaccine by representatives of Janssen; an FDA presentation of its independent review of the data submitted in support of the EUA request; and a discussion and vote by the VRBPAC.

Prior to casting their votes, committee members discussed how data from the currently ongoing Phase 3 clinical trial evaluating a two-dose schedule will impact the use of the product when authorized under the EUA as a single dose; in particular, if a two-dose regimen demonstrates improved efficacy and immunogenicity. It was thought that health policy makers, including ACIP, would have to address this issue. From a regulatory perspective, if a two-dose schedule were shown to be more effective, the EUA could be amended to authorize a two-dose schedule and/or these data could be considered under a biologics license application. Some committee members expressed concerns about the case definition used by Janssen, in particular the category of "moderate to severe" disease. It was noted that this definition is not consistent with FDA's case definitions. FDA clarified that Janssen's definition does include all severe COVID-19 disease. Because very few cases of "mild" disease were observed in the trial, operationally this definition of "moderate to severe" disease may have captured cases that would have been considered mild under other definitional frameworks. However, use of this more restrictive description of the vaccine's efficacy was considered to be reasonable.

Other members asked about the efficacy of the vaccine in participants who were SARS-CoV-2 positive at baseline. Janssen clarified that this will require further evaluation as cases in individuals seropositive at baseline were too infrequent to allow a robust analysis at this time. Additional work will also be performed to more precisely define rates of asymptomatic infections in vaccinated participants. The ability to accurately estimate efficacy against asymptomatic

infection will in part depend on whether nucleocapsid serology will allow a distinction between the SARS-CoV-2 virus and other coronaviruses.

Some committee members raised concerns about emerging variants and the data FDA would require to support authorization of a modified COVID-19 vaccine to protect against variants of concern. FDA referred to its recently revised guidance document on EUA of vaccines to prevent COVID-19, which explains that immunogenicity bridging studies could be used where the original vaccine was demonstrated to be effective in clinical trials. The ability of sera derived from participants vaccinated with the current vaccine to neutralize emerging SARS-CoV-2 variants will be important to assess. Janssen discussed preliminary data showing a drop in neutralizing ability in studies using the B.1.1.7 variant, but the drop in neutralizing activity decreases when sera are evaluated at increasing time intervals following vaccination.

FDA asked the committee members to discuss the observed vaccine efficacy estimates in participants 60 years of age and older with comorbidities. Committee members pointed out that wide confidence intervals around the point estimate of efficacy are expected as the number of COVID-19 cases is small and that these results are likely attributable to shorter follow-up times due to staged enrollment that resulted in older participants with comorbidities entering the study later. The tightening of confidence intervals and increases in point estimates for efficacy in this group in analyses that included more cases (e.g., after 14 days or those whose PCR results have not yet been centrally confirmed) were discussed. In addition, there was no evidence for decreasing efficacy as age increased, and overall efficacy among participants with comorbidities was similar to that in those without comorbidities. Additional data to further refine these efficacy estimates will be collected. Other committee members suggested that if the additional data still showed the vaccine to be less effective in this subgroup, and the two-dose study indicated greater efficacy, then older participants with comorbidities could be offered a second dose of the vaccine. Overall, committee members did not express concern about vaccine efficacy among older adults with or without comorbidities.

Committee members asked when studies in pediatric populations would begin and opined that it is important to ensure their adequate geographic representation. FDA clarified that discussions regarding studies in pediatric populations, including how to demonstrate efficacy and safety, are currently ongoing.

Following this discussion, the VRBPAC was asked to vote on whether, based on the totality of scientific evidence available, the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older.

The results of the vote were as follows: Yes: 22; No: 0; Abstain: 0

8. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the February 26, 2021 meeting, the review team concludes that:

- As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 4 of this review, it is reasonable to believe that the Janssen COVID-19 vaccine may be effective in preventing such a serious or life-threatening disease or condition that can be caused by SARS-CoV-2. Vaccine efficacy against central laboratory-confirmed, protocol-defined moderate to severe/critical COVID-19 across all geographic areas in which the trial was conducted was 66.9% (95% CI 59.0, 73.4) when considering cases occurring at least 14 days after the single-dose vaccination, and 66.1% (55.0, 74.8) when considering cases occurring at least 28 days after vaccination. VE against central laboratory-confirmed and blind-adjudicated severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination was 76.7% (54.6, 89.1) and 85.4% (54.2, 96.9), respectively. Among all hospitalizations due to COVID-19 with onset at least 14 days after vaccination, including non-centrally confirmed cases, there were 2 cases in the vaccine group (with no cases after 28 days) and 29 cases in the placebo group (with 16 cases after 28 days). As of February 5, 2021, there were 7 COVID-19-related deaths in the study in the placebo group and none in the vaccine group.

  In general, VE among the subgroups (age, comorbidity, race, ethnicity) appears to be similar to the VE in the overall study population. A lower VE estimate was observed for the subgroup of participants 60 years of age and older with comorbidities compared with the overall population, but with an observed trend of increasing VE with narrower confidence intervals as numbers of cases included in the analysis increased (i.e., counting cases from 14 days rather than 28 days and including cases not yet centrally confirmed). There were no COVID-19-related deaths and no COVID-19 cases requiring medical intervention occurring 28 days or more post-vaccination among participants age 60 years or older with medical comorbidities in the vaccine group.

  There was country-to-country variation in VE estimates for the prevention of moderate to severe/critical COVID-19 and severe/critical COVID-19, but the confidence intervals were overlapping. Predominant strains among those sequenced were Wuhan-H1 variant D614G in the United States (96.4% of sequenced cases), 20H/501Y.V2 variant (B.1.351) in South Africa (94.5% of sequenced cases), and variant of the P.2 lineage in Brazil (69.4% of sequenced cases, with the remaining 30.6% Wuhan-H1 variant D614G). There were no cases identified as B.1.1.7 or P1 lineages as of February 12, 2021.

- Based on the data summarized in Sections 4 and 5 of this review and assessment of benefits and risks in Section 6 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Known benefits are reduction in the risk of COVID-19 occurring at least 14 days and at least 28 days post-vaccination among individuals not previously infected with SARS-CoV-2, including evidence of protection against COVID-19 of any severity, protection against more severe COVID-19, and protection against COVID-19-related hospitalizations and deaths. These benefits were demonstrated in regions where SARS-CoV-2 variants of concern were circulating during the clinical trial, including the Wuhan-H1 variant D614G (predominant in the United States), B.1.351 variant (predominant in South Africa), and P.2 variant (predominant in Brazil). Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of long-term

complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission.

Known risks include common local and systemic adverse reactions (notably injection site pain, headache, myalgia, and fatigue, all of which are usually mild to moderate and lasting 1-2 days, with higher frequency in younger vaccine recipients compared with older vaccine recipients). Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up (including further evaluation of risk of thromboembolic events, tinnitus, and hypersensitivity reactions following vaccination), risks associated with vaccination of specific populations such as children younger than 18 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, and available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The review team therefore recommends issuance of an EUA for use of the Janssen COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

9. References

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10. Appendix A. Other Clinical Studies Ad26.COV2.S

Study 1001

Design: Study 1001 is an ongoing, randomized, double-blind, placebo-controlled, first-in-human Phase 1/2a study, conducted in Belgium and the United States in healthy adults ages 18 to 55 years and in adults ≥65 years in good health with and without stable underlying conditions. Participants are randomized to placebo or Ad26.COV2.S administered at either of two dose levels (5×10^{10} vp or 1×10^{11} vp) and either as a single dose or as 2 doses 56 days apart. The total study population will include 1,045 adults. By the cutoff date of January 11, 2021, the median follow-up time for participants in the 18 to 55 and ≥65 age groups were 166 and 144 days, respectively.

Objectives/Endpoints Relevant to the EUA: The primary objective is to assess the safety and reactogenicity of Ad26.COV2.S at 2 dose levels. In addition, immunogenicity of the Ad26.COV2.S regimens is being assessed. Humoral immunogenicity is assessed via SARS-CoV-2 neutralizing antibody response as measured by a wild type SARS-CoV-2 neutralization assay (wtVNA). Spike protein binding antibody responses after one vaccination are measured by S-ELISA. Cellular immunogenicity is measured by S-specific CD4+ and CD8+ T-cell responses. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Results: A single dose of Ad26.COV2.S at the 5×10^{10} vp dose level (the dose level selected for the Phase 3 studies) elicited a SARS-CoV-2 neutralizing antibody (wtVNA) and SARS-CoV-2 Spike binding antibody response that was detected by Day 15 and is increased by the Day 57 timepoint. Ad26.COV2.S was able to elicit cellular responses in participants consistent with a Th-1 phenotype. Ad26.COV2.S, given as a single dose was found to have an acceptable safety and reactogenicity profile in adults ≥18 years of age and did not raise safety concerns in any of the assessed populations.

Study 1002

Design: Study 1002 is a randomized, double-blind, placebo-controlled Phase 1, non-US IND study being conducted in Japan. The study population is comprised of healthy adults ages 20 to 55 years and ≥65 years in good health with or without stable underlying conditions. The primary objective is to assess the safety and reactogenicity of Ad26.COV2.S at two dose levels, 5×10^{10} vp and 1×10^{11} vp, administered IM with a 56-day interval. The immunogenicity of the Ad26.COV2.S regimens is also being assessed.

Results: In an interim analysis (data cutoff October 3, 2020), a single dose of Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody responses in participants 20-55 years of age by Day 29 post-vaccination, consistent with results of Study 1001. Both dose levels had acceptable tolerability and no safety concerns have been identified.

Study 2001

Design: Study 2001 is a randomized, double-blind, placebo-controlled Phase 2a study being conducted in Germany, Spain, and the Netherlands in healthy adults ≥18 to ≤55 years of age and adults in good or stable health ≥65 years of age. The study will also include a cohort of adolescents ≥12 to ≤17 years of age (not yet enrolled). Adults receive placebo or Ad26.COV2.S

at one of four dose levels: 1×10^{11} vp, 5×10^{10} vp, $2.5x10^{10}$ vp, and $1.25x10^{10}$. A target of approximately 550 adult participants will be enrolled, with approximately one third ≥65 years of age.

Objectives/Endpoints Relevant to the EUA: The study will evaluate the safety, reactogenicity, and humoral immune response of Ad26.COV2.S in 1- and 2-dose vaccination regimens followed by antigen presentation after 4 months (2-dose regimen) or 6 months (1-dose regimen).

Results: Ad26.COV2.S elicited SARS-CoV-2 neutralizing antibody responses by Day 29 post-vaccination, consistent to those of the Phase 1/2a Study 1001. No safety concerns have been identified in any of the assessed populations.

Study 3009

Design: Study 3009 is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 years of age being conducted in 10 countries. Participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection are randomized 1:1 to receive Ad26.COV2.S 5×10^{10} vp or placebo as 2-dose regimen with a 56-day interval. The objectives and endpoints are similar to those of Study 3001.

Results: Enrollment is ongoing. No safety concerns had been identified based on blinded reports of SAEs and deaths with a cutoff date of February 5, 2021.

11. Appendix B. Case Definitions for Mild COVID-19 and FDA Harmonized COVID-19

Case Definition for Mild COVID-19

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample;

AND at any time during the course of observation:

- One of the following symptoms: fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, muscle pain (myalgia), gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, new or changing olfactory or taste disorders, red or bruised looking feet or toes, or shaking chills or rigors.

A case was considered mild when it met the above case definition but not the moderate to severe/critical definition.

FDA Harmonized Case Definition for COVID-19

- A SARS-CoV-2 positive RT-PCR or molecular test result from any available respiratory tract sample (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample;

AND

- Any COVID-19 symptom: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.