

Summary Basis for Regulatory Action

Date:	08/23/2021
From:	Ramachandra Naik, PhD, Review Committee Chair, DVRPA/OVRR
BLA STN:	125742/0
Applicant:	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Submission Receipt Date:	May 18, 2021
PDUFA Action Due Date:	January 16, 2022
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	COMIRNATY
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

Director, Office of Vaccines Research and Review

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
<p>CMC</p> <ul style="list-style-type: none"> • CMC Product (OVRR) • Facilities Review (OCBQ/DMPQ) • Facilities Inspection (OCBQ/DMPQ and OVRR/DVP) • Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC) 	<p>Xiao Wang, PhD, OVRR/DVP Anissa Cheung, MSc, OVRR/DVP Kathleen Jones, PhD, OCBQ/DMPQ Laura Fontan, PhD, OCBQ/DMPQ Gregory Price, PhD, OCBQ/DMPQ CDR Donald Ertel, MS, OCBQ/DMPQ Nicole Li, MS, OCBQ/DMPQ Christian Lynch, OCBQ/DMPQ Alifiya Ghadiali, OCBQ/DMPQ Zhongren Wu, PhD, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ</p> <p>Hsiaoling Wang, PhD, OCBQ/DBSQC Emnet Yitbarek, PhD, OCBQ/DBSQC Karla Garcia, MS, OCBQ/DBSQC Anil Choudhary, PhD, MBA, OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, OCBQ/DBSQC Marie Anderson, PhD, OCBQ/DBSQC Cheryl Hulme, OCBQ/DMPQ</p>
<p>Clinical</p> <ul style="list-style-type: none"> • Clinical (OVRR) • Postmarketing Safety, Epidemiological Review (OBE/DE) • Real World Evidence • Benefit-Risk Assessment • BIMO 	<p>Susan Wollersheim, MD, OVRR/DVRPA CAPT Ann T. Schwartz, MD, OVRR/DVRPA Lucia Lee, MD, OVRR/DVRPA Deborah Thompson, MD, MSPH, OBE/DE</p> <p>Yun Lu, PhD, OBE Hong Yang, PhD, OBE Osman Yogurtcu, PhD, OBE Patrick Funk, PhD, OBE Haecin Chun, MT (ASCP) SSB, MS, OCBQ/DIS</p>
<p>Statistical</p> <ul style="list-style-type: none"> • Clinical Data (OBE/DB) • Nonclinical Data 	<p>Lei Huang, PhD, OBE/DB Ye Yang, PhD, OBE/DB Xinyu Tang, PhD, OBE/DB</p>
<p>Nonclinical/Pharmacology/Toxicology</p> <ul style="list-style-type: none"> • Toxicology (OVRR) • Developmental Toxicology (OVRR) 	<p>Nabil Al-Humadi, PhD, OVRR/DVRPA</p>
<p>Labeling</p> <ul style="list-style-type: none"> • Promotional (OCBQ/APLB) • Carton and Container Labels • Labeling Review 	<p>CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA Laura Gottschalk, PhD, OVRR/DVRPA</p>
<ul style="list-style-type: none"> • Consults (CDISC, Datasets) • Documentation Review 	<p>Brenda Baldwin, PhD, OVRR/DVRPA CAPT Michael Smith, PhD, OVRR/DVRPA</p>
<p>Advisory Committee Summary</p>	<p>No Advisory Committee meeting held</p>

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1. Introduction

BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.) submitted a Biologics License Application (BLA) STN BL 125742 for licensure of COVID-19 Vaccine, mRNA. The proprietary name of the vaccine is COMIRNATY. COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 3 weeks apart.

COMIRNATY (also referred to as BNT162b2 in this document) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((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.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type (b) (4) glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately in 2 mL glass vials manufactured by (b) (4) and in 10 mL vials manufactured by (b) (4). The diluent is stored at 20°C to 25°C and will be shipped in parallel with shipments of COMIRNATY, with arrivals synchronized so that the diluent is delivered before the vaccine is delivered. Healthcare providers may also use other sources of sterile 0.9% Sodium Chloride Injection, USP as a diluent for COMIRNATY, if necessary.

The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. The vial must be warmed to room temperature for dilution. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contain six doses of 0.3 mL of vaccine. Each 0.3 mL dose of COMIRNATY contains 30 µg of mRNA encoding the spike glycoprotein of SARS-CoV-2 and 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, 2.52 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. After dilution, the vials are stored at 2°C to 25°C and must be used within 6 hours from the time of dilution. COMIRNATY is preservative-free.

The expiry dating period for COMIRNATY Multiple Dose Vial is 9 months from the date of manufacture when stored at -90°C to -60°C. The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at (b) (4) (b) (4), the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer (b) (4) (b) (4), it is defined as the date of the (b) (4).

2. Background

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. 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). 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). SARS-CoV-2 is the causative agent 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.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of August 2021, has caused approximately 208 million cases of COVID-19, including 4.3 million deaths worldwide. In the United States (U.S.), more than 37 million cases have

been reported to the Centers for Disease Control and Prevention (CDC), of which 90% have occurred in individuals 16 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 and emerging variants has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

In the U.S., there are no licensed vaccines or anti-viral drugs for the prevention of COVID-19. In December 2020, the FDA issued emergency use authorizations (EUAs) for two mRNA vaccines which encode the SARS-CoV-2 spike glycoprotein: Pfizer-BioNTech COVID-19 Vaccine (manufactured by Pfizer, Inc. in partnership with BioNTech manufacturing GmbH) for use in individuals 16 years of age and older, and Moderna COVID-19 Vaccine (manufactured by ModernaTX, Inc.) for use in individuals 18 years of age and older. In February 2021, the FDA issued an EUA for a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike glycoprotein, manufactured by Janssen Biotech, Inc. (Janssen COVID-19 Vaccine) for use in individuals 18 years of age and older. In May 2021, the FDA expanded the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine to include adolescents 12 through 15 years of age. 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.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (Written Responses)	April 6, 2020 (Part 1) April 10, 2020 (Part 2)
2. IND submission	April 22, 2020
3. Fast Track designation granted	July 7, 2020
4. Submission of EUA request for individuals ≥16 years of age	November 20, 2020
5. Issuance of EUA for individuals ≥16 years	December 11, 2020
6. Submission of EUA request for individuals 12-15 years of age	April 9, 2021
7. Issuance of EUA for individuals 12-15 years of age	May 10, 2021
8. Pre-BLA meeting (Written Responses)	Clinical: March 9, 2021 CMC: March 31, 2021
9. BLA STN 125742/0 received	May 18, 2021
10. BLA filed	July 15, 2021
11. Mid-Cycle communication	The Applicant canceled
12. Late-Cycle meeting	The Applicant canceled
13. Action Due Date	January 16, 2022

3. Chemistry, Manufacturing and Controls (CMC)

a. Product Quality

COMIRNATY Manufacturing Overview

COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((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. COMIRNATY is supplied as a frozen suspension to be diluted with a diluent, 0.9% Sodium Chloride Injection, USP, that is supplied separately or can be acquired elsewhere, if necessary. Manufacture of the mRNA drug substance will take place in (b) (4). The final formulated drug product will be manufactured, filled, finished, labeled and packaged in (b) (4). The 0.9% Sodium Chloride Injection, USP diluent will be manufactured by (b) (4) (b) (4)

The mRNA in COMIRNATY is a single-stranded, 5'-capped mRNA encoding the full-length SARS-CoV-2 spike glycoprotein derived from the Wuhan-Hu-1 isolate (GenBank MN908947.3 and GenBank QHD43416.1). The antigen-coding RNA sequence is codon-optimized and contains two proline mutations ((b) (4)), which ensures an antigenically optimal trimerized pre-fusion conformation (S-2P). The RNA also contains common structural elements, including 5'-cap, 5'-UTR, 3'-UTR, and poly(A) tail, all of which are designed for mediating high RNA stability and translation efficiency. During RNA transcription, (b) (4) is replaced with the (b) (4). This nucleoside substitution has been demonstrated to enhance translation of *in vitro* transcribed mRNA while reducing its reactogenicity.

Drug Substance (DS)

The manufacture of mRNA DS is divided into (b) (4) major manufacturing process stages:

(b) (4)

Drug Product (DP)

The manufacturing process of the DP is divided into the following critical steps:

- **Preparation of the DS:** (b) (4)
- **Formation of LNP:** In this step, (b) (4)
- **Formulation of the bulk DP:** The bulk DP is formulated by (b) (4)
- **Filling:** The bulk DP is sterile filtered and aseptically filled into 2 mL Type (b) (4) borosilicate glass vials manufactured by (b) (4)
- **Labeling and storage:** The filled vials are visually inspected, labeled, and frozen at -90°C to -60°C.

Composition

The composition of the formulation of COMIRNATY and the function of the ingredients are provided in Table 2.

Table 2. Composition of COMIRNATY Multiple Dose Vial

Ingredients	Quantity after Dilution (per vial)	Function
SARS-CoV-2 spike glycoprotein mRNA (UNII: 5085ZFP6SJ)	225 µg	Active Ingredient
(b) (4) [4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) (UNII: (b) (4)	3.23 mg	Lipid component
(b) (4) [2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide] (UNII:(b) (4)	0.4 mg	Lipid component
DSPC [1,2-distearoyl-sn-glycero-3-phosphocholine] (UNII: 043IPI2M0K)	0.7 mg	Lipid component
Cholesterol (UNII: 97C5T2UQ7J)	1.4 mg	Lipid component
Potassium chloride (UNII: 660YQ98I10)	0.07 mg	Excipient
Monobasic potassium phosphate (UNII: 4J9FJ0HL51)	0.07 mg	Excipient
Sodium Chloride	2.7 mg	Excipient

Ingredients	Quantity after Dilution (per vial)	Function
(UNII: 451W47IQ8X)		
Dibasic sodium phosphate dihydrate (UNII: GR686LBA74)	0.49 mg	Excipient
Sucrose (UNII: C151H8M554)	46.0 mg	Excipient
(b) (4) (UNII: (b) (4))	0.450 mL	Excipient

UNII: Unique Ingredient Identifier

Stability of COMIRNATY in Multiple Dose Vial

For the long-term storage condition study, parameters monitored are Appearance, (b) (4) by (b) (4) LNP (b) (4) (b) (4) RNA content and (b) (4) (b) (4) Assay, Lipid ((b) (4) , DSPC, and Cholesterol) Content by (b) (4) (b) (4) , Container closure integrity test by (b) (4) (b) (4) Endotoxin content by (b) (4) , and Sterility.

The stability data provided in the submission support a dating period of 9 months from the date of manufacture when stored at -90°C to -60°C for the COMIRNATY DP filled in 2 mL Type (b) borosilicate glass vials. Stability data on emergency use and process performance qualification lots also support storage at -20°C ± 5°C for up to 2 weeks as well as short term storage at 5°C ± 3°C for up to one month (within the 9-month expiry dating period).

The Diluent for COMIRNATY

The contents of the vaccine vial are diluted with sterile 0.9% Sodium Chloride Injection, USP. Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. The provided diluent or another sterile 0.9% Sodium Chloride Injection, USP should be used as the diluent.

The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as cartons of 10 mL single-use vials manufactured by (b) (4) (NDC (b) (4)), or 2 mL single-use vials manufactured by (b) (4) (NDC (b) (4)). The composition of the saline diluent and the function of the ingredients are provided in Table 3.

Table 3. Composition of the Diluent

Ingredients	Quantity (per 0.3 mL dose)	Function
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.16 mg	Excipient
Water for Injection (UNII: 059QF0K00R)	0.3 mL	Excipient

UNII: Unique Ingredient Identifier

COMIRNATY

Product Composition

COMIRNATY Multiple Dose Vial is supplied as a frozen suspension that is diluted at the time of use with 1.8 mL of saline diluent. A single dose of COMIRNATY contains 30 ug mRNA in a volume of 0.3 mL, and it does not contain preservative. [See section 10.b regarding exception to the 21 CFR 610.15(a) requirement for a preservative.]

Stability of COMIRNATY

The Applicant conducted in-use stability studies to support the maximum temperature and time period that COMIRNATY can retain its physicochemical properties. Based on the data generated, COMIRNATY retains its quality attributes for up to 6 hours when stored between 2°C to 25°C (35°F to 77°F).

The carton labels and the Package Insert (PI) state that after dilution, vials should be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, exposure to room light should be minimized, and direct exposure to sunlight and ultraviolet light should be avoided. Any vaccine remaining in vials must be discarded after 6 hours and cannot be refrozen.

Assays used in clinical studies

Diagnostic Assays Used to Support Clinical Efficacy Endpoints

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 a rapid, automated *in vitro* diagnostic test for the qualitative detection of the N and E gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens collected from patients suspected of having COVID-19. This assay is used to assess viral infection of the participants before vaccination and to confirm COVID-19 cases during study follow-up.

The Roche Elecsys Anti-SARS-CoV-2 assay is a rapid, automated *in vitro* diagnostic test for detecting the presence of antibodies to nucleocapsid (N) protein of SARS-CoV-2 (antigen not present in COMIRNATY) in serum or plasma samples. This is a qualitative assay marketed as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, which would indicate a recent or prior infection. This assay is used to assess serostatus of the participants 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 uses in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

Immunogenicity Assays Used for Exploratory Immunogenicity Endpoints

Two immunogenicity assays (SARS-CoV-2 mNeonGreen (mNG) virus microneutralization assay and (b) (4) direct Luminex assay (dLIA) for IgG

quantification) were used for evaluating the immune responses from clinical trial samples.

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.

The (b) (4) S1 IgG dLIA measures IgG antibody levels to the subunit 1 (S1) of the SARS-CoV-2 spike protein in human serum samples. Qualification data provided in the submission support the (b) (4) dLIA for quantification of human IgG antibodies that bind to the S1 protein of SARS-CoV-2 and confirm that the assay is suitable for its intended use.

b. Testing Specifications

Specifications and Methods

The tests and specifications applied for routine release of COMIRNATY are shown in Table 4.

Table 4. Control of COMIRNATY: Tests and Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) (b) (4)	May contain white to off-white opaque, amorphous particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
LNP (b) (4)	(b) (4)	(b) (4)
LNP (b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4) assay	(b) (4)
RNA content	(b) (4) assay	(b) (4)
(b) (4) content	(b) (4)	(b) (4)
(b) (4) content	(b) (4)	(b) (4)
DSPC content	(b) (4)	(b) (4)
Cholesterol content	(b) (4)	(b) (4)
Vial content (volume)	Container content	Not less than (b) (4)
Lipid identities	(b) (4)	(b) (4) , Cholesterol, DSPC)

Quality Attribute	Analytical Procedure	Acceptance Criteria
Identity of encoded RNA	(b) (4)	Identity confirmed
(b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxin	Endotoxin (b) (4) (b) (4)	(b) (4)
Sterility	Sterility ((b) (4))	No Growth Detected
Container Closure Integrity	(b) (4)	Pass

Abbreviations: LNP = Lipid nanoparticles (b) (4)

The analytical methods and their validations and/or qualifications for the COMIRNATY DS and DP were found to be adequate for their intended use.

c. CBER Lot Release


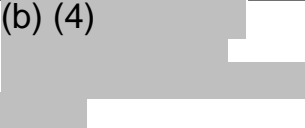

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of COMIRNATY are listed in Table 5 below. The activities performed and inspectional histories are also noted in Table 5 and are further described in the paragraphs that follow.

Table 5. Facilities involved in the manufacture of COMIRNATY

Name/address	FEI Number	DUNS number	Inspection/waiver	Results/Justification
<p>Pfizer Inc. (b) (4) (b) (4) (b) (4) Manufacture <i>Drug Substance</i> Release and stability testing <i>Drug Product</i> Release and stability testing</p>	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) NAI
<p>(b) (4) (b) (4) (b) (4) <i>Drug Substance</i> Manufacture, release and stability testing <i>Drug Product</i> Release and stability testing</p>	(b) (4)	(b) (4)	Pre-License Inspection	CBER Pre-license inspection (b) (4) VAI
<p>(b) (4) (b) (4) (b) (4) <i>Drug Product</i> LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing</p>	(b) (4)	(b) (4)	Waiver	ORA/OBPO Surveillance (b) (4) VAI
<p>Pfizer (b) (4) (b) (4) (b) (4) <i>Drug Product</i> LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing</p>	(b) (4)	(b) (4)	Pre-license inspection	CBER Pre-license inspection (b) (4) NAI

Name/address	FEI Number	DUNS number	Inspection/waiver	Results/Justification
Pfizer (b) (4)  <i>Drug Product</i> Release and stability testing	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) VAI
(b) (4)  <i>Drug Product</i> Release testing (sterility)	(b) (4)	(b) (4)	Waiver	CDER Pre-approval inspection (b) (4) VAI
(b) (4)  <i>Drug Product</i> Release testing (sterility)	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) VAI

ORA conducted a surveillance inspection of Pfizer Inc., (b) (4) from (b) (4) No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CDER conducted a pre-license inspection (PLI) of (b) (4) (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA conducted a surveillance inspection of (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a PLI of Pfizer (b) (4) from (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA conducted a surveillance inspection of Pfizer (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection of (b) (4) from (b) (4) (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) from (b) (4) (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The COMIRNATY drug product is filled and stored at -90°C to -60°C in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap. The glass vials are supplied by (b) (4)

(b) (4) The stopper and caps are supplied by (b) (4), respectively.

Pfizer performed container closure integrity testing (CCIT) on the filled 2 mL glass vials using a (b) (4) test method. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Toxicology

For the nonclinical safety evaluation, COMIRNATY was evaluated in two repeat dose toxicity studies in Wistar Han rats and a Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) in Wistar Han rats.

The repeat dose toxicity evaluations were conducted on COMIRNATY and a similar vaccine termed BNT162b2 (V8). COMIRNATY and BNT162b2 (V8) have identical amino acid sequences of the encoded antigens but COMIRNATY includes the presence of optimized codons to improve antigen expression. The IM route of exposure was selected as it is the route of clinical administration. Generation of an immune response to COMIRNATY was confirmed in rats in both repeat-dose toxicity studies. In both repeat-dose toxicity studies, administration of COMIRNATY by IM injection to male and female rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Edema and erythema at the injection sites, transient elevation in body temperature, elevations in white blood cells and acute phase reactants and decreased albumin:globulin ratios were observed. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations.

For the Combined Fertility and Developmental Study, COMIRNATY was administered to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). There were some effects (change in body weight and food consumption and effects localized to the injection site) observed in rats in these studies following administration of COMIRNATY that were not considered adverse and a relationship to COMIRNATY was not established. There were no effects on mating performance, fertility, or any ovarian or uterine parameters nor on embryo-fetal or postnatal survival, growth, or development in the offspring. An immune response was observed in female rats following administration of each vaccine candidate and these responses were also detectable in the offspring (fetuses and pups).

Nonclinical Pharmacology and Pharmacokinetics

COMIRNATY was evaluated in nonclinical pharmacology studies using animal models of mice, rats and nonhuman primates (NHP). The data from these studies indicate: (1) strong antigen-binding IgG and high titer neutralizing antibodies in mice, rat and rhesus macaques; (2) Th1-biased CD4+ T-cell response and IFN γ +, CD8+ T-cell response to BNT162b2 in both mouse and NHP studies; and (3) protection of rhesus macaques from an infectious SARS-CoV-2 challenge, with reduced detection of viral RNA in the BNT162b2-immunized animals as compared with the control-immunized macaques.

Nonclinical pharmacokinetics (PK) evaluation included (1) biodistribution of COMIRNATY using (b) (4) expressing RNA as a surrogate reporter in (b) (4) mice and in rats, and (2) the biodistribution and metabolism of the two novel lipids ((b) (4)) contained in COMIRNATY in *in vitro* studies and in a PK study in rats following administration of (b) (4) expressing RNA encapsulated in LNPs made with radiolabeled lipid markers. The study results indicate that following IM injection, the RNA encapsulated in LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. The metabolism of (b) (4) was evaluated *in vitro* using blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys and humans and *in vivo* by examining the plasma, urine, feces, and liver samples from the PK study in rats. Approximately 50% of (b) (4) is excreted unchanged in feces, while metabolism appears to play a role in the elimination of (b) (4).

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral immune responses to COMIRNATY, were obtained in the clinical studies. The data demonstrated that COMIRNATY induces a humoral immune response against the SARS-CoV-2 spike protein. The exact immunologic mechanism that confers protection against SARS-CoV-2 is unknown.

6. Clinical/Statistical

a. Clinical Program

Overview

The Applicant included data from two clinical studies in the BLA. The clinical studies which will be discussed in this SBRA are shown in Table 6.

Table 6. Overview of Clinical Studies

Study ID	C4591001	BNT162-01
NCT ID	04368728	04380701
Phase	1/2/3	1/2
Countries	Argentina, Brazil, Germany, South Africa, Turkey, U.S.	Germany
Enrollment	Phase 1: 30 participants Phase 2/3: 43,847 participants	24
Age	16 - 85 YOA	18 - 85 YOA
Purpose	Evaluate VE for prevention of COVID-19 (pivotal clinical endpoint study)	Evaluate safety and immunogenicity

Study ID	C4591001	BNT162-01
Control	Saline Placebo	None
Groups	Phase 2/3: 2 groups, randomized 1:1 to receive COMIRNATY or Placebo IM	1 group, randomized received COMIRNATY IM
Schedule	D0, D21	D0, D21
Total follow-up	6 Months (follow-up ongoing)	6 Months (follow-up ongoing)

YOA: years of age; VE: vaccine efficacy; IM: intramuscular; D: day

Study C4591001

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blind Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the U.S. for vaccine candidate and dosage selection, as well as evaluation of immunogenicity and preliminary efficacy. The protocol was expanded to include a Phase 2/3 portion of the study to evaluate clinical disease efficacy endpoint in individuals 12 years of age and older in the U.S. and additional sites outside of the U.S.

The Phase 1 portion of the study was designed to identify a preferred vaccine candidate, vaccine dose, and administration schedule for further development based on the vaccine's safety, tolerability, and immunogenicity. To this end, two age groups were evaluated in separate cohorts, younger adults 18 through 55 years of age (N=45) and older adults 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 increasing dose levels (10, 20 and 30 µg) with progression to higher dose levels in a stepwise manner. Evaluation of increasing doses in the older age group (65 through 85 years) was based on recommendations from an internal review committee that reviewed safety and immunogenicity data derived from adults 18 through 55 years of age. For each vaccine candidate and dose, 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 the Phase 1 portion of Study C4591001, in combination with data from Study BNT162-01, supported the final vaccine candidate, dose and dosing regimen (BNT162b2 administered at 30 µg, given 3 weeks apart) to proceed to the Phase 2/3 portion of Study C4591001.

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) with the goal for the older age strata to consist of 40% of the entire study population. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study; thus, the age strata were revised as follows: 16 through 55 years of age, and 56 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, 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 COMIRNATY or placebo, 3 weeks apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity of the vaccine in 360

participants in the early stage of Phase 2/3, 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 COMIRNATY for the prevention of COVID-19 occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's blinded 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 (mid-turbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (i.e., 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 was 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 included a planned interim analysis of the first primary efficacy endpoint (the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination) at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases). All primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued. Participants are expected to participate for a maximum of approximately 26 months.

Per protocol, since December 14, 2020, following issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine, 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.

The study was unblinded in stages as all ongoing participants were either individually unblinded (when eligible per local recommendations) or the subject had concluded their 6-month post-Dose 2 study visit. Participants 16 years of age and older who participated in the Phase 2/3 study were given the opportunity to receive COMIRNATY no later than the 6-month timepoint after the second study vaccination. Participants who originally received placebo but received COMIRNATY were moved to a new visit schedule to receive both doses of COMIRNATY, 3 weeks apart.

The primary safety and efficacy endpoints were:

1. Primary safety endpoint (descriptive): Solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic adverse events (AE) (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), unsolicited AEs, serious adverse events (SAEs).

2. First primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.
3. Second primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with and without serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

The pertinent secondary endpoint was:

1. Severe COVID-19 incidence per 1000 person-years of follow-up.

Study C4591001 results

The population in the protocol-specified, event-driven final 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. 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% (95% credible interval: 90.0, 97.9), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. This protocol-specified, event-driven final primary efficacy analysis was the basis for issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020.

Therefore, the primary study objective of VE against COVID-19 was met as the point estimate was above 50% and the lower bound of the 95% CI of the point estimate of VE was above 30%.

The population for the updated vaccine efficacy analysis per protocol included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to ~6 months of follow-up after Dose 2. Overall, 60.8% of participants in the COMIRNATY group and 58.7% of participants in the placebo group had ≥ 4 months of follow-up time after Dose 2 in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in participants without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19.

The updated vaccine efficacy information is presented in Tables 7a and 7b.

Table 7a: First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N ^a =19,993 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Placebo N ^a =20,118 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI ^e)
All participants	77 6.092 (19,711)	833 5.857 (19,741)	91.1 (88.8, 93.1)
16 through 64 years	70 4.859 (15,519)	709 4.654 (15,515)	90.5 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)

* 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 7b: First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N ^a =21,047 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Placebo N ^a =21,210 Cases n1 ^b Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI ^e)
All participants	81 6.340 (20,533)	854 6.110 (20,595)	90.9 (88.5, 92.8)
16 through 64 years	74 5.073 (16,218)	726 4.879 (16,269)	90.2 (87.5, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)

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

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Efficacy Against Severe COVID-19

Vaccine efficacy against severe COVID-19 for participants with or without prior SARS-CoV-2 infection is shown in Tables 8a and 8b. The VE against severe COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 95.3% (95% CI: 71.0 to 99.9) using the protocol definition of severe COVID-19 and 100.0% (95% CI: 87.6 to 100.0) based on the CDC definition of severe COVID-19.

Table 8a: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Protocol† Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1^a Surveillance Time^b (n2^c)	Placebo Cases n1^a Surveillance Time^b (n2^c)	Vaccine Efficacy % (95% CI^d)
7 days after Dose 2 ^d	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)

Table 8b: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Centers for Disease Control and Prevention (CDC)‡ Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1^a Surveillance Time^b (n2^c)	Placebo Cases n1^a Surveillance Time^b (n2^c)	Vaccine Efficacy % (95% CI^d)
7 days after Dose 2 ^d	0 6.345 (20,513)	31 6.225 (20,593)	100 (87.6, 100.0)

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

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

† Severe illness from COVID-19 is defined in the protocol as confirmed COVID-19 and presence of at least 1 of the following:

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

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

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

a. n1 = Number of participants meeting the endpoint definition.

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

c. n2 = Number of participants at risk for the endpoint.

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

Study BNT162-01

Study BNT162-01 is an ongoing Phase 1/2, open-label, dose-finding study to evaluate the safety and immunogenicity of several candidate vaccines, including BNT162b2 (1, 3, 10, 20, and 30 µg), conducted in Germany in healthy and immunocompromised adults. Only safety and immunogenicity data in individuals 16 years of age and older, the population for the intended use and who received the final vaccine formulation (30 µg BNT162b2) are used to support this application. The 30 µg dosage of BNT162b2 was administered to 12 adults 18 to 55 years of age and 12 adults 56 to 85 years of age.

The primary objective was to evaluate the safety of the BNT162 candidate vaccines. Secondary and exploratory objectives were to describe humoral and cellular immune responses following vaccination, measured at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as the safety monitoring in study C4591001.

The study started April 23, 2020. The BLA contains safety data (reactogenicity and AE analyses) up to 1 month after Dose 2 (data cutoff date: October 23, 2020), neutralizing antibody data up to ~2 months after Dose 2 (data cutoff date: October 23, 2020), and T-cell data up to ~6 months after Dose 2 (data cutoff date: March 2, 2021).

Study BNT162-01 Results

Disposition of 30 µg BNT162b2 group:

- Safety: Of a total of 24 participants, 12 participants 18 to 55 years of age and 12 participants 56 to 85 years of age completed the visit at 1- month post-Dose 2.
- Immunogenicity: Of the 12 participants, serum neutralizing antibody and T-cell responses were available for 10 and 12 participants, respectively.

Safety: The safety profiles for adult participants 18-55 and 56-85 years of age receiving 30 µg BNT162b2 in this study were similar to age-matched participants in study C4591001.

Immunogenicity: Dose-dependent increases were noted 42 days after Dose 2, compared to SARS-CoV-2 neutralizing GMTs at baseline (pre-Dose 1), and most pronounced at the 30 µg dose level. The Th1 polarization of the T-helper response was indicated by IFN γ and IL-2 production, and only minimal IL-4 production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation.

Review of the safety and immunogenicity from Phase 1 part of Study C4591001, in combination with data from Study BNT162-01, supported selection of the final vaccine candidate and dose level (BNT162b2 at 30 µg, given as two doses 3 weeks apart) to proceed into Phase 2/3 part of Study C4591001.

Lot Consistency

Consistency of process performance qualification (PPQ) batches manufactured at both Pfizer (b) (4) was demonstrated by verifying process parameters and in-process testing results as well as DP release testing. Data obtained from the analytical comparability assessments on the PPQ batches manufactured at both sites

provide evidence of reproducible and consistent manufacture of COMIRNATY DP of acceptable product quality across all supply nodes.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for a total of nine (9) clinical study sites that participated in the conduct of study Protocol C4591001. Three (3) of these inspection assignments focused on clinical study sites that enrolled the pediatric population and six (6) of the study sites enrolled the adult population. The inspections did not reveal findings that impact the BLA.

c. Pediatrics

The Applicant's Pediatric Plan was presented to the FDA Pediatric Review Committee (PeRC) on August 3, 2021. The committee agreed with the Applicant's request for a deferral for studies in participants 0 to <16 years of age because the biological product is ready for approval for use in individuals 16 years of age and older before pediatric studies in participants 0 to <16 years of age are completed (Section 505B(a)(3)(A)(i) of PREA).

The PREA-required studies specified in the approval letter and agreed upon with the Applicant are as follows:

1. Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age
2. Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age
3. Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

7. Safety and Pharmacovigilance

The most commonly reported ($\geq 10\%$) solicited adverse reactions in COMIRNATY recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported ($\geq 10\%$) solicited adverse reactions in COMIRNATY recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

follow-up after Dose 2. There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY.

From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the COMIRNATY group and 17 in the placebo group. None of the deaths were considered related to vaccination.

Since the issuance of the EUA (December 11, 2020), post-authorization safety data has been reported from individuals 16 years of age and older following any dose of COMIRNATY. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Below are presented adverse reactions categorized as important identified risks in the pharmacovigilance plan that have occurred during the conduct of the clinical trial and have been reported following the issuance of the EUA.

Myocarditis/Pericarditis

During the time from Dose 1 to unblinding in Study C4591001, one report of pericarditis was identified in the COMIRNATY group, occurring in a male participant ≥ 55 years of age, with no medical history, 28 days after Dose 2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. One report of myocarditis was identified in a male participant < 55 years of age in the placebo group, occurring 5 days after his second placebo dose.

Post-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of COMIRNATY. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (65 cases per million doses administered as per CDC communication on August 20, 2021), particularly following the second dose, and onset of symptoms within 7 days following vaccination. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals. A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

These safety findings of increased risk for myocarditis/pericarditis led to warning in section 5.2 Warning and Precautions of the PI.

Myocarditis and pericarditis are considered important identified risks in the pharmacovigilance plan included in the BLA. Of note, the Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis as well as an unexpected serious risk for subclinical myocarditis (see Section 11c Recommendation for Postmarketing Activities, for study details).

Moreover, since vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA undertook a quantitative benefit-risk assessment to model the excess risk of myocarditis/pericarditis vs. the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths. For estimation of risk, the model took a conservative approach by relying on non-chart-confirmed cases from a US healthcare claims database (OPTUM) that could provide a control group and greater confidence in denominators for vaccine exposures. Thus, the estimates of excess risk in this model are higher than the rates estimated from reports to VAERS (an uncontrolled passive surveillance system), with an estimated excess risk approaching 200 cases per million vaccinated males 16-17 years of age (the age/sex-stratified group with the highest risk). For estimation of benefit, the model output was highly dependent on the assumed COVID-19 incidence, as well as assumptions about vaccine efficacy and duration of protection. The assessment therefore considered a range of scenarios including but not limited to a “most likely” scenario associated with recent Delta variant surge and diminished vaccine effectiveness (70% overall, 80% against COVID-19 hospitalization) compared to that observed in the clinical trial. The “worst-case” scenario with low COVID-19 incidence reflecting the July 2021 nadir and the same somewhat diminished vaccine effectiveness as in the “most likely” scenario.

For males and females 18 years of age and older and for females 16-17 years of age, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the “most likely” scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations and deaths under the “worst case” scenario. However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. Additionally, the “worst case” scenario model predicts prevention of >13,000 cases of non-hospitalized COVID-19 per million vaccinated males 16-17 years of age, which would include prevention of clinically significant morbidity and/or long-term sequelae associated with some of these cases. Finally, the model does not account for indirect societal/public health benefits of vaccination. Considering these additional factors, FDA concluded that even under the “worst case” scenario the benefits of vaccination sufficiently outweigh risks to support approval of the vaccine in males 16-17 years of age.

Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements) and through continued safety surveillance and postmarketing studies to further assess and understand these risks, including an immunogenicity and safety study of lower dose levels of COMIRNATY in individuals 12 through <30 years of age. The Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis (see section 11c for study details).

Anaphylaxis

The risk of anaphylaxis was recognized early in the post-authorization time period and it is included as an important identified risk in the PVP. The estimated crude reporting rate for anaphylaxis is 6.0 cases per million doses. Therefore, the incidence of anaphylaxis after receipt of COMIRNATY is comparable with those reported after receipt of other vaccines.

There were no reports of anaphylaxis associated with COMIRNATY in clinical study participants through the cutoff date of March 13, 2021.

A contraindication for individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY is included in section 4 of the PI. Additionally, a warning statement is included in section 5.1 of the PI instructing 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 COMIRNATY”

Pharmacovigilance Plan (PVP)

The Applicant’s proposed pharmacovigilance plan (version 1.1) includes the following important risks and missing information:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Use in pediatric individuals <12 years of age

In addition to routine pharmacovigilance, the Applicant will conduct the postmarketing studies listed in Section 11c Recommendation for Postmarketing Activities.

Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 11c are adequate to monitor the postmarketing safety for COMIRNATY.

8. Labeling

The proprietary name, COMIRNATY, was reviewed by CBER’s Advertising and Promotional Labeling Branch (APLB) on July 2, 2021, and found to be acceptable. CBER communicated this decision to the Applicant on July 6, 2021. The APLB found the PI and package/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from “COVID-19 mRNA vaccine (nucleoside-modified)” to “COVID-19 Vaccine, mRNA” and including a warning for an increased risk of myocarditis and pericarditis following administration of COMIRNATY. All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant.

9. Advisory Committee Meetings

Vaccines and Related Biological Products Committee (VRBPAC) meetings were convened on October 22, 2020 to discuss, in general, development for EUA and licensure of vaccines to prevent COVID-19 and on December 10, 2020, to discuss BioNTech Manufacturing GmbH/Pfizer's EUA request for the Pfizer-BioNTech COVID-19 Vaccine.

On October 22, 2020, the VRBPAC was presented with the following items for discussion (no vote):

1. Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.
2. Please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine.
3. Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to
 - a. Further evaluate safety, effectiveness and immune markers of protection
 - b. Evaluate the safety and effectiveness in specific populations

In general, the VRBPAC endorsed FDA's approach and recommendations on the safety and effectiveness data necessary to support a BLA and EUA for COVID-19 vaccines as outlined in the respective guidance documents. VRBPAC members recommended for the median follow-up of 2 month to be the minimum follow-up period and suggested longer follow-up periods to evaluate, both safety and efficacy, if feasible. The VRBPAC endorsed the importance of additional studies to further evaluate safety and effectiveness of the vaccine after EUA issuance and/or licensure and underscored the need to evaluate the safety and effectiveness of COVID-19 vaccines in specific populations.

On December 10, 2020, VRBPAC discussed Pfizer- BioNTech Manufacturing GmbH's EUA request for their vaccine to prevent COVID-19 in individuals 16 years of age and older. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy study C4591001.

The VRPBAC voted on one question:

1. Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?

The results of the vote were as follows:

Yes = 17 No = 4 Abstain = 1

The VRBPAC was presented with the following items for discussion (no vote):

1. 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.

2. 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 COVID-19 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 BLA. The VRBPAC commented on the need to further assess vaccine effect on asymptomatic infection and viral shedding, and further evaluation of safety and effectiveness in subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2.

FDA did not refer this application to the VRBPAC because our review of the information submitted to this BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

a. Identification of BLA Lots

Upon CBER's request inquiring about what BLA-compliant EUA-labeled lots may be available for use upon licensure of COMIRNATY, the Applicant submitted information listing which lots they considered to be manufactured according to the BLA. To address the issue of these lots not bearing the vial label associated with BLA approval, CBER worked with the Applicant to develop a Dear HCP letter to be included with lots considered by CBER to be BLA-compliant. This letter explained that some lots labeled for EUA use were also considered BLA-compliant and refers HCP to a website for additional information. CBER requested and the Applicant agreed that only EUA-labeled lots that had also undergone CBER lot release according to the BLA would be considered BLA-compliant and listed at the website included in the Dear HCP letter.

b. Exception to the 21 CFR 610.15(a) Requirement for a Preservative

Under 21 CFR 610.15(a), a vaccine product in multiple-dose containers must (absent certain exceptions) contain a preservative. The Applicant submitted a request for exception to this requirement and provided a justification for the multi-dose presentation of COMIRNATY not containing a preservative. CBER considered the Applicant's request for an exception to the 21 CFR 610.15(a) for COMIRNATY as a multiple dose preservative-free presentation acceptable.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of COMIRNATY for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of COMIRNATY that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk/benefit balance for COMIRNATY is favorable and supports approval for use in individuals 16 years of age and older.

c. Recommendation for Postmarketing Activities

BioNTech Manufacturing GmbH has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

1. Study C4591009, entitled “A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

Final Protocol Submission: August 31, 2021
Monitoring Report Submission: October 31, 2022
Interim Report Submission: October 31, 2023
Study Completion: June 30, 2025
Final Report Submission: October 31, 2025

2. Study C4591021, entitled “Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

Final Protocol Submission: August 11, 2021
Progress Report Submission: September 30, 2021
Interim Report 1 Submission: March 31, 2022
Interim Report 2 Submission: September 30, 2022
Interim Report 3 Submission: March 31, 2023
Interim Report 4 Submission: September 30, 2023
Interim Report 5 Submission: March 31, 2024
Study Completion: March 31, 2024
Final Report Submission: September 30, 2024

3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

Final Protocol Submission: January 31, 2022
Study Completion: March 31, 2024
Final Report Submission: September 30, 2024

4. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network)

Final Protocol Submission: November 30, 2021
Study Completion: December 31, 2026
Final Report Submission: May 31, 2027

5. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age

Final Protocol Submission: September 30, 2021
Study Completion: November 30, 2023
Final Report Submission: May 31, 2024

6. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age

Final Protocol Submission: November 30, 2021
Study Completion: June 30, 2022
Final Report Submission: December 31, 2022

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

7. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry”

Final Protocol Submission: July 1, 2021
Study Completion: June 1, 2025
Final Report Submission: December 1, 2025

8. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age

Final Protocol Submission: September 30, 2021
Study Completion: November 30, 2023
Final Report Submission: May 31, 2024

9. Study C4591012, entitled “Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran’s Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine”

Final Protocol Submission: January 29, 2021
Study Completion: June 30, 2023
Final Report Submission: December 31, 2023

10. Study C4591014, entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California”

Final Protocol Submission: March 22, 2021
Study Completion: December 31, 2022
Final Report Submission: June 30, 2023

PEDIATRIC REQUIREMENTS

11. Deferred pediatric study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age

Final Protocol Submission: October 7, 2020
Study Completion: May 31, 2023
Final Report Submission: October 31, 2023

12. Deferred pediatric study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age

Final Protocol Submission: February 8, 2021
Study Completion: November 30, 2023
Final Report Submission: May 31, 2024

13. Deferred pediatric study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

Final Protocol Submission: January 31, 2022
Study Completion: July 31, 2024
Final Report Submission: October 31, 2024