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SECRETARY OF DEFENSE
1000 DEFENSE PENTAGON
WASHINGTON, DC 20301-1000

AUG 24 2021

MEMORANDUM FOR SENIOR PENTAGON LEADERSHIP
COMMANDERS OF THE COMBATANT COMMANDS
DEFENSE AGENCY AND DOD FIELD ACTIVITY DIRECTORS

SUBJECT: Mandatory Coronavirus Disease 2019 Vaccination of Department of Defense Service Members

To defend this Nation, we need a healthy and ready force. After careful consultation with medical experts and military leadership, and with the support of the President, I have determined that mandatory vaccination against coronavirus disease 2019 (COVID-19) is necessary to protect the Force and defend the American people.

Mandatory vaccinations are familiar to all of our Service members, and mission-critical inoculation is almost as old as the U.S. military itself. Our administration of safe, effective COVID-19 vaccines has produced admirable results to date, and I know the Department of Defense will come together to finish the job, with urgency, professionalism, and compassion.

I therefore direct the Secretaries of the Military Departments to immediately begin full vaccination of all members of the Armed Forces under DoD authority on active duty or in the Ready Reserve, including the National Guard, who are not fully vaccinated against COVID-19.

Service members are considered fully vaccinated two weeks after completing the second dose of a two-dose COVID-19 vaccine or two weeks after receiving a single dose of a one-dose vaccine. Those with previous COVID-19 infection are not considered fully vaccinated.

Mandatory vaccination against COVID-19 will only use COVID-19 vaccines that receive full licensure from the Food and Drug Administration (FDA), in accordance with FDA-approved labeling and guidance. Service members voluntarily immunized with a COVID-19 vaccine under FDA Emergency Use Authorization or World Health Organization Emergency Use Listing in accordance with applicable dose requirements prior to, or after, the establishment of this policy are considered fully vaccinated. Service members who are actively participating in COVID-19 clinical trials are exempted from mandatory vaccination against COVID-19 until the trial is complete in order to avoid invalidating such clinical trial results.

Mandatory vaccination requirements will be implemented consistent with DoD Instruction 6205.02, "DoD Immunization Program," July 23, 2019. The Military Departments should use existing policies and procedures to manage mandatory vaccination of Service members to the extent practicable. Mandatory vaccination of Service members will be subject to any identified contraindications and any administrative or other exemptions established in Military Department policy. The Military Departments may promulgate appropriate guidance to carry out the requirements set out above. The Under Secretary of Defense for Personnel and



OSD007764-21/CMD010116-21

Readiness may provide additional guidance to implement and comply with FDA requirements or Centers for Disease Control and Prevention recommendations.

The Secretaries of the Military Departments should impose ambitious timelines for implementation. Military Departments will report regularly on vaccination completion using established systems for other mandatory vaccine reporting.

Our vaccination of the Force will save lives. Thank you for your focus on this critical mission.



ASSISTANT SECRETARY OF DEFENSE

**1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200**

HEALTH AFFAIRS

**MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND
RESERVE AFFAIRS
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND
RESERVE AFFAIRS
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER
AND RESERVE AFFAIRS
DIRECTOR, DEFENSE HEALTH AGENCY**

**SUBJECT: Mandatory Vaccination of Service Members using the Pfizer-BioNTech COVID-19
and Comirnaty COVID-19 Vaccines**

On August 23, 2021, the U.S. Food and Drug Administration (FDA) approved the biologics license application for the Comirnaty vaccine, made by Pfizer-BioNTech, as a two-dose series for prevention of coronavirus disease 2019 (COVID-19) in persons aged 16 years or older. Previously, on December 11, 2020, the FDA issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine, which has the same formulation as the Comirnaty vaccine. Per FDA guidance, these two vaccines are "interchangeable" and DoD health care providers should "use doses distributed under the EUA to administer the vaccination series as if the doses were the licensed vaccine."

Consistent with FDA guidance, DoD health care providers will use both the Pfizer-BioNTech COVID-19 vaccine and the Comirnaty COVID-19 vaccine interchangeably for the purpose of vaccinating Service members in accordance with Secretary of Defense Memorandum, "Mandatory Coronavirus Disease 2019 Vaccination of Department of Defense Service Members," August 24, 2021.

My point of contact for this guidance is Colonel Michael J. Berecz, who may be reached at (703) 681-8463 or michael.j.berecz.mil@mail.mil.

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**Terry Adirim, M.D., M.P.H., M.B.A.
Acting**

**cc:
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Joint Staff Surgeon**

¹ FDA, "Q&A for Comirnaty (COVID-19 Vaccine mRNA)," <https://www.fda.gov/vaccines-blood-biologics/qa-comirnaty-covid-19-vaccine-mrna>, accessed September 10, 2021.

Excerpt From:

**IN THE UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF FLORIDA
PENSACOLA DIVISION**

JOHN DOE #1-#14 and JANE D

Plaintiffs,

v. Case No. 3:21-cv-1211-AW-HTC

**LLOYD AUSTIN, III, in his official OE
capacity as Secretary of Defense, et al.,**

Defendants.

ORDER DENYING PRELIMINARY INJUNCTION MOTIONS

Next, to the extent plaintiffs rely on the administrative record to support their claim (*e.g.*, ECF No. 3-2 at 20 (“[T]here is no indication in the record”)), I note that the administrative record is not before the court. Finally, the plaintiffs’ argument that the mandate is arbitrary and capricious because it “relied on facially unlawful

FDA actions” (ECF No. 3-2 at 20) cannot succeed because plaintiffs have not shown those actions were facially unlawful. *See infra*. This is not to say that the plaintiffs’ challenge cannot ultimately succeed, but at this stage, they have not shown enough.

- 3. The plaintiffs next argue that the mandate violates their statutory right to refuse an EUA vaccine. ECF No. 3-2 at 20-21. Under the EUA statute, recipients of EUA drugs must be “informed . . . of the option to accept or refuse administration of the product.” 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(III); *see also* 5 U.S.C. § 706(2)(C) (APA provision prohibiting agency action taken “in excess of statutory jurisdiction, authority, or limitations, or short of statutory right”). And under 10 U.S.C. § 1107a, “[i]n the case of the administration of [an EUA] product . . . to members of the armed forces,” that statutory right to refuse “may be waived only by the President only if the President determines, in writing, that complying with such requirement is not in the interests of national security.” 10 U.S.C. § 1107a(a)(1). The DOD acknowledges that the President has not executed a waiver under this section, ECF No. 45 at 52:8-9, so as things now stand, the DOD cannot mandate vaccines that only have an EUA. 10 U.S.C. § 1107a(a)(1).

One problem with this argument is that the DOD’s guidance documents explicitly say only FDA-licensed COVID-19 vaccines are mandated. *See, e.g.*, ECF No. 1-3 at 2 (DOD mandate memorandum) (“Mandatory vaccination against COVID-19 will only use COVID-19 vaccines that receive full licensure from the

[FDA] in accordance with FDA-approved labeling and guidance.”); *and* ECF No. 1- 7 at 11 (Air Force guidance) (“Only an FDA-licensed vaccine may be mandated . . .”). The plaintiffs present a facial challenge, ECF No. 33 at 10 (“Plaintiffs’ claims are facial challenges to a generally applicable military regulation . . .”), and on its face, the mandate does not require anyone to take an EUA vaccine.

Notably, though, the plaintiffs have shown that the DOD is requiring injections from vials not labeled “Comirnaty.” Indeed, defense counsel could not even say whether vaccines labeled “Comirnaty” exist at all. ECF No. 45 at 48:5-7.

(Although the DOD’s response said it had an adequate Comirnaty supply, it later clarified that it was mandating vaccines from EUA-labeled vials. *See id.* at 46:22-47:3.) In the DOD’s view, this is fine because the contents of EUA-labeled vials are chemically identical to the contents of vials labeled “Comirnaty” (if there are any such vials). According to the DOD’s argument, this means servicemembers are not required to accept “a *product* authorized for emergency use.” 10 U.S.C. § 1107a(a)(1). Rather, the DOD argues that once the FDA licensed Comirnaty, all EUA-labeled vials essentially became Comirnaty, even if not so labeled. ECF No. 45 at 60:1-3. Thus, the DOD argues, the “product” injected is a chemical formulation

that has received full FDA licensure—not merely an EUA—so § 1107a does not apply. *Id.* at 65:1-6.⁸

The DOD’s interpretation of § 1107a is unconvincing. For starters, FDA licensure does not retroactively apply to vials shipped before BLA approval. *See* 21 U.S.C. § 355(a) (“No person shall introduce . . . into interstate commerce any new drug, unless an approval of an application [for FDA licensure] *is effective* with respect to such drug.” (emphasis added)). Thus, as a legal matter, vaccines sent before August 23—and vaccines produced after August 23 in unapproved facilities—remain “product[s] authorized for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act.” § 1107a(a)(1).⁹ Section 1107a’s explicit cross-reference to the EUA provisions suggests a concern that drugs mandated for military personnel be actually BLA-approved, not merely chemically similar to a BLA-approved drug. And the distinction is more than mere labeling: to be BLA compliant, the drug must be produced at approved facilities, *see* ECF No. 1-4 at 2; 21 C.F.R. §§ 600.11, 600.20-.21, and there is no indication that all EUA-labeled

⁸The plaintiffs also cite 10 U.S.C. § 1107, but the defendants correctly note it does not apply. That statute covers “an investigational new drug or a drug

unapproved for its applied use,” and this vaccine (either under the EUA or the BLA) is neither.

⁹This distinction is the basis for the FDA’s comment that the BLA-compliant vials and the EUA-compliant vials are “legally distinct,” even though their chemical formulation is identical. *See* ECF No. 1-6 at 3 n.8. Thus, the DOD cannot rely on the FDA to find that the two drugs are legally identical for § 1107a purposes.

vials are from BLA-approved facilities.¹⁰ Moreover, the DOD concedes that some of its current vials are not BLA-compliant, and that there is no policy to ensure that servicemembers get only BLA-compliant vaccines. *See* ECF No. 45 at 61:10-12. It is difficult to see how vials that the DOD admits are not BLA-compliant—and thus could only be EUA products—could fall outside § 1107a’s prohibition on mandatory administration.

Notwithstanding all of this, the plaintiffs have not shown a substantial likelihood of success on this APA claim. The FDA’s Summary Basis for Regulatory Action approving Comirnaty explains that certain lots of EUA-labeled vials are nonetheless “BLA-compliant,” and that healthcare providers may disregard the EUA-specific labeling when administering doses from those vials. ECF No. 1-5 at 28. The DOD claims it possesses “hundreds of thousands of BLA-compliant vaccine doses that are EUA-labeled, and is using them.” ECF No. 30-14 ¶ 18. If the DOD is, in fact, administering Comirnaty (albeit EUA-labeled Comirnaty), the plaintiffs’

§ 1107a issue disappears. Although there is apparently no DOD policy in place to ensure that servicemembers receive BLA-compliant vaccines, *see* ECF No. 45 at

¹⁰The FDA's Comirnaty approval letter redacts the approved manufacturing locations, *see* ECF No. 1-4 at 2, and the EUA extension letter does not identify which facilities were "identified and agreed upon" in Pfizer's EUA application, ECF No. 1- 6 at 8. The Summary Basis for Regulatory Action suggests that not all Pfizer facilities are BLA compliant, because it contemplates that not all EUA-labeled lots will contain BLA-compliant vials. *See* ECF No. 1-5 at 28.

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61:10-12, no plaintiff claims he or she was specifically denied a BLA-compliant dose or offered only a dose from a non-BLA-compliant vial. Because the plaintiffs have not shown they are (or will be) required to receive an EUA-labeled, non-BLA compliant vaccine, the plaintiffs have not shown a likelihood of

success.¹¹ **B.**

The plaintiffs' APA claims against the FDA do not fare better. These claims break down into three categories. First, plaintiffs contend the FDA's Comirnaty approval is invalid because the FDA did not follow the Food, Drug & Cosmetic Act (FDCA) and the Public Health Service Act (PHSA). Second, the plaintiffs argue that the FDA wrongfully determined that EUA drugs and Comirnaty are interchangeable.

¹¹ The plaintiffs argue that the FDA cannot allow BLA-compliant vaccine doses to bear an EUA label. ECF No. 33 at 24-25. But they cite no legal authority for this proposition, and they do not dispute that the FDA’s Summary Basis for Regulatory Action specifically included certain EUA-labeled lots under the BLA approval. Regardless, the plaintiffs do not present this claim against the FDA. j

Still, the statutes leave unclear what FDA labeling decisions are discretionary. The FDA’s Comirnaty approval letter says that the labeling on Comirnaty vials “must be identical” to what Pfizer submitted in its application, ECF No. 1-4 at 4, but this label does not appear to be identical to an EUA label, *see* ECF No. 1-5 at 28. And federal regulations require the FDA commissioner to initiate license revocation proceedings if he determines that a licensed product is “misbranded with respect to any [of its intended uses]” or “fails to conform to the applicable standards established in the license . . . designed to ensure the continued safety, purity, and potency” of the product. 21 C.F.R. § 601.5(b)(1)(iv), (vi). These provisions could be read to prohibit distributing a fully licensed drug with an EUA-specific label and package insert rather than those its BLA approval require.

Summary Basis for Regulatory Action

Date:	11/8/2021
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 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately in 2 mL glass vials manufactured by Fresenius Kabi LLC and in 10 mL vials manufactured by Hospira, Inc. 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 Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer-Manufacturing Belgium NV in Puurs, Belgium, 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 Andover, MA, USA. The final formulated drug product will be manufactured, filled, finished, labeled and packaged in Puurs, Belgium or in Kalamazoo, MI, USA. The 0.9% Sodium Chloride Injection, USP diluent will be manufactured by Fresenius-Kabi USA, LLC ((b) (4)) and Hospira, Inc. ((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) 87P), 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 I 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	Amount per vial	Function
SARS-CoV-2 spike glycoprotein mRNA (UNII: 5085ZFP6SJ)	225 µg	Active Ingredient
ALC-0315 [4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) (UNII: AVX8DX713V)	3.23 mg	Lipid component
ALC-0159 [2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide] (UNII: PJH39UMU6H)	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	Amount per vial	Function
(UNII: 451W47IQ8X)		
Dibasic sodium phosphate dihydrate (UNII: GR686LBA74)	0.49 mg	Excipient
Sucrose (UNII: C151H8M554)	46.0 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	q.s.	Excipient

UNII: Unique Ingredient Identifier

q.s. = quantum satis (as much as may suffice)

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), RNA content and (b) (4) Assay, Lipid (ALC-0315, ALC-0159, DSPC, and Cholesterol) Content by (b) (4), Container closure integrity test by (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 I 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 Hospira, Inc (NDC 0409-4888-10), or 2 mL single-use vials manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02). 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: 059QF0KO0R)	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 µg 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)
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)
ALC-0315 content	(b) (4)	(b) (4)
ALC-0159 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) (ALC-0315, ALC-0159, 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. 875 Chesterfield Parkway West Chesterfield, MO 63017</p> <p>(b) (4) Manufacture</p> <p><i>Drug Substance</i> Release and stability testing</p> <p><i>Drug Product</i> Release and stability testing</p>	1940118	004954111	Waiver	ORA Surveillance August 19-20, 2019 NAI
<p>Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burt Road Andover, MA 01810</p> <p><i>Drug Substance</i> Manufacture, release and stability testing</p> <p><i>Drug Product</i> Release and stability testing</p>	1222181	174350868	Pre-License Inspection	CBER Pre-license inspection July 19-23, 2021 VAI
<p>Pharmacia & Upjohn Company LLC 7000 Portage Road Kalamazoo, MI 49001</p> <p><i>Drug Product</i> LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing</p>	1810189	618054084	Waiver	ORA/OBPO Surveillance May 11-20, 2021 VAI
<p>Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium</p> <p><i>Drug Product</i> LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing</p>	1000654629	370156507	Pre-license inspection	CBER Pre-license inspection June 24-July 2, 2021 NAI

Name/address	FEI Number	DUNS number	Inspection/waiver	Results/Justification
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland <i>Drug Product</i> Release and stability testing	3004145594	985586408	Waiver	ORA Surveillance November 4-12, 2019 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., Chesterfield, MO, from August 19 – 20, 2019. No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CBER conducted a pre-license inspection (PLI) of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC from July 19 – 23, 2021. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA conducted a surveillance inspection of Pharmacia & Upjohn Company LLC from May 11 – 20, 2021. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER conducted a PLI of Pfizer Manufacturing Belgium NV from June 24 - July 2, 2021. No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA conducted a surveillance inspection of Pfizer Ireland Pharmaceuticals from November 4 – 12, 2019. All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection of (b) (4) from (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). 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)

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 (ALC-0315 and ALC-0159) 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 ALC-0315 and ALC-0159 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 ALC-0159 is excreted unchanged in feces, while metabolism appears to play a role in the elimination of ALC-0315.

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.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

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.

- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

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 Puurs and Pfizer Kalamazoo 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%).

Among participants 16 through 55 years of age who had received at least 1 dose of COMIRNATY (N=12,995) or placebo (N=13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 103 (0.8%) COMIRNATY recipients and 117 (0.9%) placebo recipients. In a similar analysis in participants 56 years of age and older (COMIRNATY=8,931, placebo=8,895), serious adverse events were reported by 165 (1.8%) COMIRNATY recipients and 151 (1.7%) placebo recipients who received at least 1 dose of COMIRNATY or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of

follow-up after Dose 2. 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

**5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT
REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021**

Report Prepared by:

Worldwide Safety

Pfizer

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LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AESI	adverse event of special interest
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DLP	data lock point
EUA	emergency use authorisation
HLGT	(MedDRA) High Group Level Term
HLT	(MedDRA) High Level Term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
PCR	Polymerase Chain Reaction
PT	(MedDRA) Preferred Term
PVP	pharmacovigilance plan
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
RSI	reference safety information
TME	targeted medically event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standardised MedDRA query
SOC	(MedDRA) System Organ Class
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	vaccine adverse event reporting system

1. INTRODUCTION

Reference is made to the Request for Comments and Advice submitted 04 February 2021 regarding Pfizer/BioNTech's proposal for the clinical and post-authorization safety data package for the Biologics License Application (BLA) for our investigational COVID-19 Vaccine (BNT162b2). Further reference is made to the Agency's 09 March 2021 response to this request, and specifically, the following request from the Agency.

“Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission.”

This document provides an integrated analysis of the cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through 28 February 2021.

2. METHODOLOGY

Pfizer is responsible for the management post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these

proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of adverse event reports (AERs) does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.
- Among adverse event reports received into the Pfizer safety database during the cumulative period, only those having a complete workflow cycle in the safety database (meaning they progressed to Distribution or Closed workflow status) are included in the monthly SMSR. This approach prevents the inclusion of cases that are not fully processed hence not accurately reflecting final information. Due to the large numbers of spontaneous adverse event reports received for the product, the MAH has prioritised the processing of serious cases, in order to meet expedited regulatory reporting timelines and ensure these reports are available for signal detection and evaluation activity. The increased volume of reports has not impacted case processing for serious reports, and compliance metrics continue to be monitored weekly with prompt action taken as needed to maintain compliance with expedited reporting obligations. Non-serious cases are entered into the safety database no later than 4 calendar days from receipt. Entrance into the database includes the coding of all adverse events; this allow for a manual review of events being received but may not include immediate case processing to completion. Non-serious cases are processed as soon as possible and no later than 90 days from receipt. Pfizer has also taken a multiple actions to help alleviate the large increase of adverse event reports. This includes significant technology enhancements, and process and workflow solutions, as well as increasing the number of data entry and case processing colleagues. To date, Pfizer has onboarded approximately (b) (4) additional full-time employees (FTEs). More are joining each month with an expected total of more than (b) (4) additional resources by the end of June 2021.

3. RESULTS

3.1. Safety Database

3.1.1. General Overview

It is estimated that approximately (b) (4) doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 February 2021.

Cumulatively, through 28 February 2021, there was a total of 42,086 case reports (25,379 medically confirmed and 16,707 non-medically confirmed) containing 158,893 events. Most cases (34,762) were received from United States (13,739), United Kingdom (13,404) Italy (2,578), Germany (1913), France (1506), Portugal (866) and Spain (756); the remaining 7,324 were distributed among 56 other countries.

Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

	Characteristics	Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17	175 ^a
	18-30	4953
	31-50	13886
	51-64	7884
	65-74	3098
	≥ 75	5214
	Unknown	6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

As shown in [Figure 1](#), the System Organ Classes (SOCs) that contained the greatest number ($\geq 2\%$) of events, in the overall dataset, were General disorders and administration site conditions (51,335 AEs), Nervous system disorders (25,957), Musculoskeletal and connective tissue disorders (17,283), Gastrointestinal disorders (14,096), Skin and subcutaneous tissue disorders (8,476), Respiratory, thoracic and mediastinal disorders (8,848), Infections and infestations (4,610), Injury, poisoning and procedural complications (5,590), and Investigations (3,693).

Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness

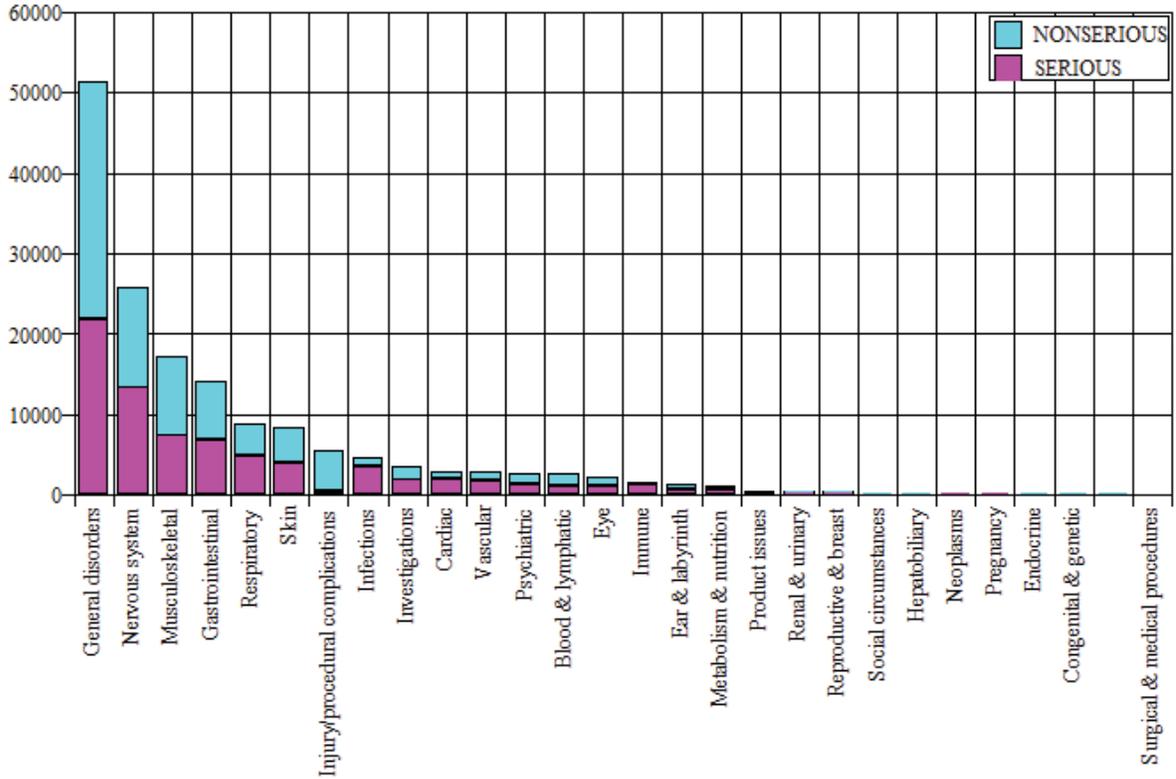


Table 2 shows the most commonly ($\geq 2\%$) reported MedDRA (v. 23.1) PTs in the overall dataset (through 28 February 2021),

Table 2. Events Reported in $\geq 2\%$ Cases

MedDRA SOC	MedDRA PT	Cumulatively Through 28 February 2021 AEs (AERP%) N = 42086
Blood and lymphatic system disorders		
	Lymphadenopathy	1972 (4.7%)
Cardiac disorders		
	Tachycardia	1098 (2.6%)
Gastrointestinal disorders		
	Nausea	5182 (12.3%)
	Diarrhoea	1880 (4.5%)
	Vomiting	1698 (4.0%)
General disorders and administration site conditions		
	Pyrexia	7666 (18.2%)
	Fatigue	7338 (17.4%)
	Chills	5514 (13.1%)
	Vaccination site pain	5181 (12.3%)

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Table 2. Events Reported in $\geq 2\%$ Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	MedDRA PT	AEs (AERP%) N = 42086
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		93473

3.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan**Table 3. Safety concerns**

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in Pregnancy and lactation Use in Paediatric Individuals <12 Years of Age Vaccine Effectiveness

Table 4. Important Identified Risk

Topic	Description														
Important Identified Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)														
Anaphylaxis	<p>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm. These cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the Table below:</p> <table border="1" data-bbox="423 569 1276 768"> <thead> <tr> <th>Brighton Collaboration Level</th> <th>Number of cases</th> </tr> </thead> <tbody> <tr> <td>BC 1</td> <td>290</td> </tr> <tr> <td>BC 2</td> <td>311</td> </tr> <tr> <td>BC 3</td> <td>10</td> </tr> <tr> <td>BC 4</td> <td>391</td> </tr> <tr> <td>BC 5</td> <td>831</td> </tr> <tr> <td><i>Total</i></td> <td>1833</td> </tr> </tbody> </table> <p>Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as “reported event of anaphylaxis with insufficient evidence to meet the case definition” and Level 5 as not a case of anaphylaxis.</p> <p>There were 1002 cases (54.0% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4:</p> <p>Country of incidence: UK (261), US (184), Mexico (99), Italy (82), Germany (67), Spain (38), France (36), Portugal (22), Denmark (20), Finland, Greece (19 each), Sweden (17), Czech Republic , Netherlands (16 each), Belgium, Ireland (13 each), Poland (12), Austria (11); the remaining 57 cases originated from 15 different countries.</p> <p>Relevant event seriousness: Serious (2341), Non-Serious (617);</p> <p>Gender: Females (876), Males (106), Unknown (20);</p> <p>Age (n=961) ranged from 16 to 98 years (mean = 54.8 years, median = 42.5 years);</p> <p>Relevant even outcome^a: fatal (9)^b, resolved/resolving (1922), not resolved (229), resolved with sequelae (48), unknown (754);</p> <p>Most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), and Lip swelling (64).</p> <p>Conclusion: Evaluation of BC cases Level 1 - 4 did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.</p>	Brighton Collaboration Level	Number of cases	BC 1	290	BC 2	311	BC 3	10	BC 4	391	BC 5	831	<i>Total</i>	1833
Brighton Collaboration Level	Number of cases														
BC 1	290														
BC 2	311														
BC 3	10														
BC 4	391														
BC 5	831														
<i>Total</i>	1833														

a Different clinical outcome may be reported for an event that occurred more than once to the same individual.

b There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths

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Table 5. Important Potential Risk

Topic	Description
Important Potential Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	<p>No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful observed/expected analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continues to accrue.</p> <p>The search criteria utilised to identify potential cases of VAED for this report includes PTs indicating a lack of effect of the vaccine and PTs potentially indicative of severe or atypical COVID-19^a.</p> <p>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 138 cases [0.33% of the total PM dataset], reporting 317 potentially relevant events were retrieved:</p> <p>Country of incidence: UK (71), US (25), Germany (14), France, Italy, Mexico, Spain, (4 each), Denmark (3); the remaining 9 cases originated from 9 different countries; Cases Seriousness: 138; Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38). Gender: Females (73), Males (57), Unknown (8); Age (n=132) ranged from 21 to 100 years (mean = 57.2 years, median = 59.5); Case outcome: fatal (38), resolved/resolving (26), not resolved (65), resolved with sequelae (1), unknown (8); Of the 317 relevant events, the most frequently reported PTs (≥2%) were: Drug ineffective (135), Dyspnoea (53), Diarrhoea (30), COVID-19 pneumonia (23), Vomiting (20), Respiratory failure (8), and Seizure (7).</p> <p>Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life-threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD.</p> <p>In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.</p>

a. Search criteria: Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Use in Pregnancy and lactation	<ul style="list-style-type: none"> • Number of cases: 413^a (0.98% of the total PM dataset); 84 serious and 329 non-serious; • Country of incidence: US (205), UK (64), Canada (31), Germany (30), Poland (13), Israel (11); Italy (9), Portugal (8), Mexico (6), Estonia, Hungary and Ireland, (5 each), Romania (4), Spain (3), Czech Republic and France (2 each), the remaining 10 cases were distributed among 10 other countries. <p>Pregnancy cases: 274 cases including:</p> <ul style="list-style-type: none"> • 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins). • Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted). • 146 non-serious mother cases reported exposure to vaccine in utero without the occurrence of any clinical adverse event. The exposure PTs coded to the PTs Maternal exposure during pregnancy (111), Exposure during pregnancy (29) and Maternal exposure timing unspecified (6). Trimester of exposure was reported in 21 of these cases: 1st trimester (15 cases), 2nd trimester (7), and 3rd trimester (2). • 124 mother cases, 49 non-serious and 75 serious, reported clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases coded to the PTs Abortion spontaneous (25), Uterine contraction during pregnancy, Premature rupture of membranes, Abortion, Abortion missed, and Foetal death (1 each). Other clinical events which occurred in more than 5 cases coded to the PTs Headache (33), Vaccination site pain (24), Pain in extremity and Fatigue (22 each), Myalgia and Pyrexia (16 each), Chills (13) Nausea (12), Pain (11), Arthralgia (9), Lymphadenopathy and Drug ineffective (7 each), Chest pain, Dizziness and Asthenia (6 each), Malaise and COVID-19 (5 each). Trimester of exposure was reported in 22 of these cases: 1st trimester (19 cases), 2nd trimester (1 case), 3rd trimester (2 cases). • 4 serious foetus/baby cases reported the PTs Exposure during pregnancy, Foetal growth restriction, Maternal exposure during pregnancy, Premature baby (2 each), and Death neonatal (1). Trimester of exposure was reported for 2 cases (twins) as occurring during the 1st trimester. <p>Breast feeding baby cases: 133, of which:</p> <ul style="list-style-type: none"> • 116 cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical adverse events; • 17 cases, 3 serious and 14 non-serious, reported the following clinical events that occurred in the infant/child exposed to vaccine via breastfeeding: Pyrexia (5), Rash (4), Infant irritability (3), Infantile vomiting, Diarrhoea, Insomnia, and Illness (2 each), Poor feeding infant, Lethargy, Abdominal discomfort, Vomiting, Allergy to vaccine, Increased appetite, Anxiety, Crying, Poor quality sleep, Eructation, Agitation, Pain and Urticaria (1 each). <p>Breast feeding mother cases (6):</p> <ul style="list-style-type: none"> • 1 serious case reported 3 clinical events that occurred in a mother during breast feeding (PT Maternal exposure during breast feeding); these events coded to the PTs Chills, Malaise, and Pyrexia • 1 non-serious case reported with very limited information and without associated AEs.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
	<ul style="list-style-type: none"> • In 4 cases (3 non-serious; 1 serious) Suppressed lactation occurred in a breast feeding women with the following co-reported events: Pyrexia (2), Paresis, Headache, Chills, Vomiting, Pain in extremity, Arthralgia, Breast pain, Scar pain, Nausea, Migraine, Myalgia, Fatigue and Breast milk discolouration (1 each). <p>Conclusion: There were no safety signals that emerged from the review of these cases of use in pregnancy and while breast feeding.</p>
Use in Paediatric Individuals <12 Years of Age	<p style="text-align: center;"><u>Paediatric individuals <12 years of age</u></p> <ul style="list-style-type: none"> • Number of cases: 34^d (0.1% of the total PM dataset), indicative of administration in paediatric subjects <12 years of age; • Country of incidence: UK (29), US (3), Germany and Andorra (1 each); • Cases Seriousness: Serious (24), Non-Serious (10); • Gender: Females (25), Males (7), Unknown (2); • Age (n=34) ranged from 2 months to 9 years, mean = 3.7 years, median = 4.0; • Case outcome: resolved/resolving (16), not resolved (13), and unknown (5). • Of the 132 reported events, those reported more than once were as follows: Product administered to patient of inappropriate age (27, see Medication Error), Off label use (11), Pyrexia (6), Product use issue (5), Fatigue, Headache and Nausea (4 each), Vaccination site pain (3), Abdominal pain upper, COVID-19, Facial paralysis, Lymphadenopathy, Malaise, Pruritus and Swelling (2 each). <p>Conclusion: No new significant safety information was identified based on a review of these cases compared with the non-paediatric population.</p>
Vaccine Effectiveness	<p>Company conventions for coding cases indicative of lack of efficacy:</p> <p>The coding conventions for lack of efficacy in the context of administration of the COVID-19 vaccine were revised on 15 February 2021, as shown below:</p> <ul style="list-style-type: none"> • PT “Vaccination failure” is coded when ALL of the following criteria are met: <ul style="list-style-type: none"> ○ The subject has received the series of two doses per the dosing regimen in local labeling. ○ At least 7 days have elapsed since the second dose of vaccine has been administered. ○ The subject experiences SARS-CoV-2 infection (confirmed laboratory tests). • PT “Drug ineffective” is coded when either of the following applies: <ul style="list-style-type: none"> ○ The infection is not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied, e.g., “the vaccine did not work”, “I got COVID-19”. ○ It is unknown: <ul style="list-style-type: none"> ▪ Whether the subject has received the series of two doses per the dosing regimen in local labeling; ▪ How many days have passed since the first dose (including unspecified number of days like” a few days”, “some days”, etc.); ▪ If 7 days have passed since the second dose; ○ The subject experiences a vaccine preventable illness 14 days after receiving the first dose up to and through 6 days after receipt of the second dose. <p>Note: after the immune system as had sufficient time (14 days) to respond to the vaccine, a report of COVID-19 is considered a potential lack of efficacy even if the vaccination course is not complete.</p> <p>Summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date:</p>

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Table 6. Description of Missing Information

Topic	Description		
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)		
	1st dose (day 1-13)	From day 14 post 1st dose to day 6 post 2nd dose	Day 7 post 2nd dose
	Code only the events describing the SARS-CoV-2 infection	Code “Drug ineffective”	Code “Vaccination failure”
	Scenario Not considered LOE	Scenario considered LOE as “Drug ineffective”	Scenario considered LOE as “Vaccination failure”
	<p>Lack of efficacy cases</p> <ul style="list-style-type: none"> • Number of cases: 1665^b (3.9 % of the total PM dataset) of which 1100 were medically confirmed and 565 non medically confirmed; • Number of lack of efficacy events: 1665 [PT: Drug ineffective (1646) and Vaccination failure (19)^f]. • Country of incidence: US (665), UK (405), Germany (181), France (85), Italy (58), Romania (47), Belgium (33), Israel (30), Poland (28), Spain (21), Austria (18), Portugal (17), Greece (15), Mexico (13), Denmark (8), Canada (7), Hungary, Sweden and United Arab Emirates (5 each), Czech Republic (4), Switzerland (3); the remaining 12 cases originated from 9 different countries. • COVID-19 infection was suspected in 155 cases, confirmed in 228 cases, in 1 case it was reported that the first dose was not effective (no other information). • COVID-19 infection (suspected or confirmed) outcome was reported as resolved/resolving (165), not resolved (205) or unknown (1230) at the time of the reporting; there were 65 cases where a fatal outcome was reported. <p>Drug ineffective cases (1649)</p> <ul style="list-style-type: none"> • Drug ineffective event seriousness: serious (1625), non-serious (21)^e; • Lack of efficacy term was reported: <ul style="list-style-type: none"> ○ after the 1st dose in 788 cases ○ after the 2nd dose in 139 cases ○ in 722 cases it was unknown after which dose the lack of efficacy occurred. • Latency of lack of efficacy term reported after the first dose was known for 176 cases: <ul style="list-style-type: none"> ○ Within 9 days: 2 subjects; ○ Within 14 and 21 days: 154 subjects; ○ Within 22 and 50 days: 20 subjects; • Latency of lack of efficacy term reported after the second dose was known for 69 cases: <ul style="list-style-type: none"> ○ Within 0 and 7 days: 42 subjects; ○ Within 8 and 21 days: 22 subjects; ○ Within 23 and 36 days: 5 subjects. • Latency of lack of efficacy term reported in cases where the number of doses administered was not provided, was known in 409 cases: <ul style="list-style-type: none"> ○ Within 0 and 7 days after vaccination: 281 subjects. ○ Within 8 and 14 days after vaccination: 89 subjects. ○ Within 15 and 44 days after vaccination: 39 subjects. <p>According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 1649 cases where lack of efficacy was reported after the 1st dose or the</p>		

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
	<p>2nd dose, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness.</p> <p style="text-align: center;"><i>Vaccination failure cases (16)</i></p> <ul style="list-style-type: none"> • Vaccination failure seriousness: all serious; • Lack of efficacy term was reported in all cases after the 2nd dose; • Latency of lack of efficacy was known for 14 cases: <ul style="list-style-type: none"> ○ Within 7 and 13 days: 8 subjects; ○ Within 15 and 29 days: 6 subjects. <p>COVID-19 (10) and Asymptomatic COVID-19 (6) were the reported vaccine preventable infections that occurred in these 16 cases.</p> <p>Conclusion: No new safety signals of vaccine lack of efficacy have emerged based on a review of these cases.</p>

- a. From a total of 417 cases, 4 cases were excluded from the analysis. In 3 cases, the MAH was informed that a 33-year-old and two unspecified age pregnant female patients were scheduled to receive bnt162b2 (PT reported Off label use and Product use issue in 2 cases; Circumstance or information capable of leading to medication error in one case). One case reported the PT Morning sickness; however, pregnancy was not confirmed in this case.
- b. 558 additional cases retrieved in this dataset were excluded from the analysis; upon review, 546 cases cannot be considered true lack of efficacy cases because the PT Drug ineffective was coded but the subjects developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine; in 5 cases the PT Drug ineffective was removed after data lock point (DLP) because the subjects did not develop COVID-19 infection; in 1 case, reporting Treatment failure and Transient ischaemic attack, the Lack of efficacy PT did not refer to BNT162b2 vaccine; 5 cases have been invalidated in the safety database after DLP; 1 case has been deleted from the discussion because the PTs reported Pathogen resistance and Product preparation issue were not indicative of a lack of efficacy. to be eliminated.
- c. Upon review, 31 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects
- d. Upon review, 28 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects.
- e. Different clinical outcomes may be reported for an event that occurred more than once to the same individual
- f. In 2 cases the PT Vaccination failure was replaced with Drug ineffective after DLP. Another case was not included in the discussion of the Vaccination failure cases because correct scheduling (21 days apart between the first and second dose) cannot be confirmed.

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3.1.3. Review of Adverse Events of Special Interest (AESIs)

Please refer to [Appendix 1](#) for the list of the company’s AESIs for BNT162b2.

The company’s AESI list takes into consideration the lists of AESIs from the following expert groups and regulatory authorities: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general.

The AESI list is comprised of MedDRA PTs, HLTs, HLTs or MedDRA SMQs and can be changed as appropriate based on the evolving safety profile of the vaccine.

Table 7 provides a summary review of cumulative cases within AESI categories in the Pfizer safety database. This is distinct from safety signal evaluations which are conducted and included, as appropriate, in the Summary Monthly Safety Reports submitted regularly to the FDA and other Health Authorities.

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
Anaphylactic Reactions <i>Search criteria: Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	Please refer to the Risk ‘Anaphylaxis’ included above in Table 4 .
Cardiovascular AESIs <i>Search criteria: PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i>	<ul style="list-style-type: none"> • Number of cases: 1403 (3.3% of the total PM dataset), of which 241 are medically confirmed and 1162 are non-medically confirmed; • Country of incidence: UK (268), US (233), Mexico (196), Italy (141), France (128), Germany (102), Spain (46), Greece (45), Portugal (37), Sweden (20), Ireland (17), Poland (16), Israel (13), Austria, Romania and Finland (12 each), Netherlands (11), Belgium and Norway (10 each), Czech Republic (9), Hungary and Canada (8 each), Croatia and Denmark (7 each), Iceland (5); the remaining 30 cases were distributed among 13 other countries; • Subjects’ gender: female (1076), male (291) and unknown (36); • Subjects’ age group (n = 1346): Adult^c (1078), Elderly^d (266) Child^e and Adolescent^f (1 each); • Number of relevant events: 1441, of which 946 serious, 495 non-serious; in the cases reporting relevant serious events; • Reported relevant PTs: Tachycardia (1098), Arrhythmia (102), Myocardial infarction (89), Cardiac failure (80), Acute myocardial infarction (41), Cardiac failure acute (11), Cardiogenic shock and Postural orthostatic tachycardia syndrome (7 each) and Coronary artery disease (6); • Relevant event onset latency (n = 1209): Range from <24 hours to 21 days, median <24 hours;

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Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Relevant event outcome^g: fatal (136), resolved/resolving (767), resolved with sequelae (21), not resolved (140) and unknown (380); <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i></p>	<ul style="list-style-type: none"> • Number of cases: 3067 (7.3% of the total PM dataset), of which 1013 are medically confirmed and 2054 are non-medically confirmed; • Country of incidence: US (1272), UK (609), Germany (360), France (161), Italy (94), Spain (69), Romania (62), Portugal (51), Poland (50), Mexico (43), Belgium (42), Israel (41), Sweden (30), Austria (27), Greece (24), Denmark (18), Czech Republic and Hungary (17 each), Canada (12), Ireland (11), Slovakia (9), Latvia and United Arab Emirates (6 each); the remaining 36 cases were distributed among 16 other different countries; • Subjects' gender: female (1650), male (844) and unknown (573); • Subjects' age group (n= 1880): Adult (1315), Elderly (560), Infant^h and Adolescent (2 each), Child (1); • Number of relevant events: 3359, of which 2585 serious, 774 non-serious; • Most frequently reported relevant PTs (>1 occurrence): COVID-19 (1927), SARS-CoV-2 test positive (415), Suspected COVID-19 (270), Ageusia (228), Anosmia (194), SARS-CoV-2 antibody test negative (83), Exposure to SARS-CoV-2 (62), SARS-CoV-2 antibody test positive (53), COVID-19 pneumonia (51), Asymptomatic COVID-19 (31), Coronavirus infection (13), Occupational exposure to SARS-CoV-2 (11), SARS-CoV-2 test false positive (7), Coronavirus test positive (6), SARS-CoV-2 test negative (3) SARS-CoV-2 antibody test (2); • Relevant event onset latency (n = 2070): Range from <24 hours to 374 days, median 5 days; • Relevant event outcome: fatal (136), not resolved (547), resolved/resolving (558), resolved with sequelae (9) and unknown (2110). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i></p>	<ul style="list-style-type: none"> • Number of cases: 20 cases (0.05% of the total PM dataset), of which 15 are medically confirmed and 5 are non-medically confirmed; • Country of incidence: UK (8), France and Poland (2 each), and the remaining 8 cases were distributed among 8 other different countries; • Subjects' gender: female (17) male and unknown (1 each); • Subjects' age group (n=19): Adult (18), Elderly (1); • Number of relevant events: 20 events, 16 serious, 4 non-serious

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Reported relevant PTs: Erythema multiforme (13) and Chillblains (7) • Relevant event onset latency (n = 18): Range from <24 hours to 17 days, median 3 days; • Relevant event outcome: resolved/resolving (7), not resolved (8) and unknown (6). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Haematological AESIs <i>Search criteria: Leukopenias NEC (HLT) (Primary Path) OR Neutropenias (HLT) (Primary Path) OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms</i></p>	<ul style="list-style-type: none"> • Number of cases: 932 (2.2 % of the total PM dataset), of which 524 medically confirmed and 408 non-medically confirmed; • Country of incidence: UK (343), US (308), France (50), Germany (43), Italy (37), Spain (27), Mexico and Poland (13 each), Sweden (10), Israel (9), Netherlands (8), Denmark, Finland, Portugal and Ireland (7 each), Austria and Norway (6 each), Croatia (4), Greece, Belgium, Hungary and Switzerland (3 each), Cyprus, Latvia and Serbia (2 each); the remaining 9 cases originated from 9 different countries; • Subjects' gender (n=898): female (676) and male (222); • Subjects' age group (n=837): Adult (543), Elderly (293), Infant (1); • Number of relevant events: 1080, of which 681 serious, 399 non-serious; • Most frequently reported relevant PTs (≥15 occurrences) include: Epistaxis (127), Contusion (112), Vaccination site bruising (96), Vaccination site haemorrhage (51), Petechiae (50), Haemorrhage (42), Haematochezia (34), Thrombocytopenia (33), Vaccination site haematoma (32), Conjunctival haemorrhage and Vaginal haemorrhage (29 each), Haematoma, Haemoptysis and Menorrhagia (27 each), Haematemesis (25), Eye haemorrhage (23), Rectal haemorrhage (22), Immune thrombocytopenia (20), Blood urine present (19), Haematuria, Neutropenia and Purpura (16 each) Diarrhoea haemorrhagic (15); • Relevant event onset latency (n = 787): Range from <24 hours to 33 days, median = 1 day; • Relevant event outcome: fatal (34), resolved/resolving (393), resolved with sequelae (17), not resolved (267) and unknown (371). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i></p>	<ul style="list-style-type: none"> • Number of cases: 70 cases (0.2% of the total PM dataset), of which 54 medically confirmed and 16 non-medically confirmed; • Country of incidence: UK (19), US (14), France (7), Italy (5), Germany (4), Belgium, Mexico and Spain (3 each), Austria, and Iceland (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (43), male (26) and unknown (1); • Subjects' age group (n=64): Adult (37), Elderly (27);

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Number of relevant events: 94, of which 53 serious, 41 non-serious; • Most frequently reported relevant PTs (≥3 occurrences) include: Alanine aminotransferase increased (16), Transaminases increased and Hepatic pain (9 each), Liver function test increased (8), Aspartate aminotransferase increased and Liver function test abnormal (7 each), Gamma-glutamyltransferase increased and Hepatic enzyme increased (6 each), Blood alkaline phosphatase increased and Liver injury (5 each), Ascites, Blood bilirubin increased and Hypertransaminasaemia (3 each); • Relevant event onset latency (n = 57): Range from <24 hours to 20 days, median 3 days; • Relevant event outcome: fatal (5), resolved/resolving (27), resolved with sequelae (1), not resolved (14) and unknown (47). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Facial Paralysis <i>Search criteria: PTs Facial paralysis, Facial paresis</i></p>	<ul style="list-style-type: none"> • Number of cases: 449ⁱ (1.07% of the total PM dataset), 314 medically confirmed and 135 non-medically confirmed; • Country of incidence: US (124), UK (119), Italy (40), France (27), Israel (20), Spain (18), Germany (13), Sweden (11), Ireland (9), Cyprus (8), Austria (7), Finland and Portugal (6 each), Hungary and Romania (5 each), Croatia and Mexico (4 each), Canada (3),Czech Republic, Malta, Netherlands, Norway, Poland and Puerto Rico (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (295), male (133), unknown (21); • Subjects' age group (n=411): Adult (313), Elderly (96), Infant^j and Child (1 each); • Number of relevant events^k: 453, of which 399 serious, 54 non-serious; • Reported relevant PTs: Facial paralysis (401), Facial paresis (64); • Relevant event onset latency (n = 404): Range from <24 hours to 46 days, median 2 days; • Relevant event outcome: resolved/resolving (184), resolved with sequelae (3), not resolved (183) and unknown (97); <p>Overall Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue. Causality assessment will be further evaluated following availability of additional unblinded data from the clinical study C4591001, which will be unblinded for final analysis approximately mid-April 2021. Additionally, non-interventional post-authorisation safety studies, C4591011 and C4591012 are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy in vaccinated individuals. The timeline for conducting these analyses will be established based on the size of the vaccinated population captured in the study data sources by the first interim reports (due 30 June</p>

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Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
Immune-Mediated/Autoimmune AESIs <i>Search criteria: Immune-mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT (Primary Path) OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i>	<p>2021). Study C4591021, pending protocol endorsement by EMA, is also intended to inform this risk.</p> <ul style="list-style-type: none"> • Number of cases: 1050 (2.5 % of the total PM dataset), of which 760 medically confirmed and 290 non-medically confirmed; • Country of incidence (>10 cases): UK (267), US (257), Italy (70), France and Germany (69 each), Mexico (36), Sweden (35), Spain (32), Greece (31), Israel (21), Denmark (18), Portugal (17), Austria and Czech Republic (16 each), Canada (12), Finland (10). The remaining 74 cases were from 24 different countries. • Subjects' gender (n=682): female (526), male (156). • Subjects' age group (n=944): Adult (746), Elderly (196), Adolescent (2). • Number of relevant events: 1077, of which 780 serious, 297 non-serious. • Most frequently reported relevant PTs (>10 occurrences): Hypersensitivity (596), Neuropathy peripheral (49), Pericarditis (32), Myocarditis (25), Dermatitis (24), Diabetes mellitus and Encephalitis (16 each), Psoriasis (14), Dermatitis Bullous (13), Autoimmune disorder and Raynaud's phenomenon (11 each); • Relevant event onset latency (n = 807): Range from <24 hours to 30 days, median <24 hours. • Relevant event outcome¹: resolved/resolving (517), not resolved (215), fatal (12), resolved with sequelae (22) and unknown (312). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
Musculoskeletal AESIs <i>Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial¹; Chronic fatigue syndrome; Polyarthritits; Polyneuropathy; Post viral fatigue syndrome; Rheumatoid arthritis</i>	<ul style="list-style-type: none"> • Number of cases: 3600 (8.5% of the total PM dataset), of which 2045 medically confirmed and 1555 non-medically confirmed; • Country of incidence: UK (1406), US (1004), Italy (285), Mexico (236), Germany (72), Portugal (70), France (48), Greece and Poland (46), Latvia (33), Czech Republic (32), Israel and Spain (26), Sweden (25), Romania (24), Denmark (23), Finland and Ireland (19 each), Austria and Belgium (18 each), Canada (16), Netherlands (14), Bulgaria (12), Croatia and Serbia (9 each), Cyprus and Hungary (8 each), Norway (7), Estonia and Puerto Rico (6 each), Iceland and Lithuania (4 each); the remaining 21 cases originated from 11 different countries; • Subjects' gender (n=3471): female (2760), male (711); • Subjects' age group (n=3372): Adult (2850), Elderly (515), Child (4), Adolescent (2), Infant (1); • Number of relevant events: 3640, of which 1614 serious, 2026 non-serious; • Reported relevant PTs: Arthralgia (3525), Arthritis (70), Rheumatoid arthritis (26), Polyarthritits (5), Polyneuropathy, Post viral fatigue syndrome, Chronic fatigue syndrome (4 each), Arthritis bacterial (1); • Relevant event onset latency (n = 2968): Range from <24 hours to 32 days, median 1 day;

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Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> Relevant event outcome: resolved/resolving (1801), not resolved (959), resolved with sequelae (49), and unknown (853). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Neurological AESIs (including demyelination)</p> <p><i>Search criteria: Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Narcolepsy</i></p>	<ul style="list-style-type: none"> Number of cases: 501 (1.2% of the total PM dataset), of which 365 medically confirmed and 136 non-medically confirmed. Country of incidence (≥9 cases): UK (157), US (68), Germany (49), Mexico (35), Italy (31), France (25), Spain (18), Poland (17), Netherlands and Israel (15 each), Sweden (9). The remaining 71 cases were from 22 different countries. Subjects' gender (n=478): female (328), male (150). Subjects' age group (n=478): Adult (329), Elderly (149); Number of relevant events: 542, of which 515 serious, 27 non-serious. Most frequently reported relevant PTs (>2 occurrences) included: Seizure (204), Epilepsy (83), Generalised tonic-clonic seizure (33), Guillain-Barre syndrome (24), Fibromyalgia and Trigeminal neuralgia (17 each), Febrile convulsion, (15), Status epilepticus (12), Aura and Myelitis transverse (11 each), Multiple sclerosis relapse and Optic neuritis (10 each), Petit mal epilepsy and Tonic convulsion (9 each), Ataxia (8), Encephalopathy and Tonic clonic movements (7 each), Foaming at mouth (5), Multiple sclerosis, Narcolepsy and Partial seizures (4 each), Bad sensation, Demyelination, Meningitis, Postictal state, Seizure like phenomena and Tongue biting (3 each); Relevant event onset latency (n = 423): Range from <24 hours to 48 days, median 1 day; Relevant events outcome: fatal (16), resolved/resolving (265), resolved with sequelae (13), not resolved (89) and unknown (161); <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Other AESIs</p> <p><i>Search criteria: Herpes viral infections (HLT) (Primary Path) OR PTs Adverse event following immunisation; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Middle East respiratory syndrome; Multiple organ dysfunction syndrome; Occupational exposure to communicable disease; Patient</i></p>	<ul style="list-style-type: none"> Number of cases: 8152 (19.4% of the total PM dataset), of which 4977 were medically confirmed and 3175 non-medically confirmed; Country of incidence (> 20 occurrences): UK (2715), US (2421), Italy (710), Mexico (223), Portugal (210), Germany (207), France (186), Spain (183), Sweden (133), Denmark (127), Poland (120), Greece (95), Israel (79), Czech Republic (76), Romania (57), Hungary (53), Finland (52), Norway (51), Latvia (49), Austria (47), Croatia (42), Belgium (41), Canada (39), Ireland (34), Serbia (28), Iceland (25), Netherlands (22). The remaining 127 cases were from 21 different countries; Subjects' gender (n=7829): female (5969), male (1860); Subjects' age group (n=7479): Adult (6330), Elderly (1125), Adolescent, Child (9 each), Infant (6);

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive</i>	<ul style="list-style-type: none"> • Number of relevant events: 8241, of which 3674 serious, 4568 non-serious; • Most frequently reported relevant PTs (≥6 occurrences) included: Pyrexia (7666), Herpes zoster (259), Inflammation (132), Oral herpes (80), Multiple organ dysfunction syndrome (18), Herpes virus infection (17), Herpes simplex (13), Ophthalmic herpes zoster (10), Herpes ophthalmic and Herpes zoster reactivation (6 each); • Relevant event onset latency (n =6836): Range from <24 hours to 61 days, median 1 day; • Relevant events outcome: fatal (96), resolved/resolving (5008), resolved with sequelae (84), not resolved (1429) and unknown (1685). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
Pregnancy Related AESIs <i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i>	<p>For relevant cases, please refer to Table 6, Description of Missing Information, Use in Pregnancy and While Breast Feeding</p>
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	<ul style="list-style-type: none"> • Number of cases: 69 cases (0.17% of the total PM dataset), of which 57 medically confirmed, 12 non-medically confirmed; • Country of incidence: Germany (17), France and UK (13 each), US (6), Belgium, Italy and Spain (4 each), Sweden (2), Austria, Canada, Denmark, Finland, Luxembourg and Norway (1 each); • Subjects' gender: female (46), male (23); • Subjects' age group (n=68): Adult (7), Elderly (60), Infant (1); • Number of relevant events: 70, all serious; • Reported relevant PTs: Acute kidney injury (40) and Renal failure (30); • Relevant event onset latency (n = 42): Range from <24 hours to 15 days, median 4 days; • Relevant event outcome: fatal (23), resolved/resolving (10), not resolved (15) and unknown (22). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT)</i>	<ul style="list-style-type: none"> • Number of cases: 130 cases (0.3% of the total PM dataset), of which 107 medically confirmed;

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Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<p><i>(Primary Path) OR Respiratory failures (excl neonatal) (HLT)</i> <i>(Primary Path) OR Viral lower respiratory tract infections (HLT)</i> <i>(Primary Path) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i></p>	<ul style="list-style-type: none"> • Countries of incidence: United Kingdom (20), France (18), United States (16), Germany (14), Spain (13), Belgium and Italy (9), Denmark (8), Norway (5), Czech Republic, Iceland (3 each); the remaining 12 cases originated from 8 different countries. • Subjects' gender (n=130): female (72), male (58). • Subjects's age group (n=126): Elderly (78), Adult (47), Adolescent (1). • Number of relevant events: 137, of which 126 serious, 11 non-serious; • Reported relevant PTs: Respiratory failure (44), Hypoxia (42), Respiratory disorder (36), Acute respiratory distress syndrome (10), Chronic respiratory syndrome (3), Severe acute respiratory syndrome (2). • Relevant event onset latency (n=102): range from < 24 hours to 18 days, median 1 day; • Relevant events outcome: fatal (41), Resolved/resolving (47), not recovered (18) and unknown (31). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Thromboembolic Events <i>Search criteria: Embolism and thrombosis (HLGT) (Primary Path), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i></p>	<ul style="list-style-type: none"> • Number of cases: 151 (0.3% of the total PM dataset), of which 111 medically confirmed and 40 non-medically confirmed; • Country of incidence: UK (34), US (31), France (20), Germany (15), Italy and Spain (6 each), Denmark and Sweden (5 each), Austria, Belgium and Israel (3 each), Canada, Cyprus, Netherlands and Portugal (2 each); the remaining 12 cases originated from 12 different countries; • Subjects' gender (n= 144): female (89), male (55); • Subjects' age group (n=136): Adult (66), Elderly (70); • Number of relevant events: 168, of which 165 serious, 3 non-serious; • Most frequently reported relevant PTs (>1 occurrence) included: Pulmonary embolism (60), Thrombosis (39), Deep vein thrombosis (35), Thrombophlebitis superficial (6), Venous thrombosis limb (4), Embolism, Microembolism, Thrombophlebitis and Venous thrombosis (3 each) Blue toe syndrome (2); • Relevant event onset latency (n = 124): Range from <24 hours to 28 days, median 4 days; • Relevant event outcome: fatal (18), resolved/resolving (54), resolved with sequelae (6), not resolved (49) and unknown (42). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents</i></p>	<ul style="list-style-type: none"> • Number of cases: 275 (0.6% of the total PM dataset), of which 180 medically confirmed and 95 non-medically confirmed; • Country of incidence: UK (81), US (66), France (32), Germany (21), Norway (14), Netherlands and Spain (11 each), Sweden (9),

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>(Primary Path) OR HLT</i> <i>Cerebrovascular venous and sinus thrombosis (Primary Path)</i>	<p>Israel (6), Italy (5), Belgium (3), Denmark, Finland, Poland and Switzerland (2 each); the remaining 8 cases originated from 8 different countries;</p> <ul style="list-style-type: none"> • Subjects' gender (n= 273): female (182), male (91); • Subjects' age group (n=265): Adult (59), Elderly (205), Child^m (1); • Number of relevant events: 300, all serious; • Most frequently reported relevant PTs (>1 occurrence) included: <ul style="list-style-type: none"> ○ PTs indicative of Ischaemic stroke: Cerebrovascular accident (160), Ischaemic stroke (41), Cerebral infarction (15), Cerebral ischaemia, Cerebral thrombosis, Cerebral venous sinus thrombosis, Ischaemic cerebral infarction and Lacunal infarction (3 each) Basal ganglia stroke, Cerebellar infarction and Thrombotic stroke (2 each); ○ PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage (26), Haemorrhagic stroke (11), Haemorrhage intracranial and Subarachnoid haemorrhage (5 each), Cerebral haematoma (4), Basal ganglia haemorrhage and Cerebellar haemorrhage (2 each); • Relevant event onset latency (n = 241): Range from <24 hours to 41 days, median 2 days; • Relevant event outcome: fatal and resolved/resolving (61 each), resolved with sequelae (10), not resolved (85) and unknown (83). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Vasculitic Events <i>Search criteria: Vasculitides HLT</i>	<ul style="list-style-type: none"> • Number of cases: 32 cases (0.08% of the total PM dataset), of which 26 medically confirmed and 6 non-medically confirmed; • Country of incidence: UK (13), France (4), Portugal, US and Spain (3 each), Cyprus, Germany, Hungary, Italy and Slovakia and Costa rica (1 each); • Subjects' gender: female (26), male (6); • Subjects' age group (n=31): Adult (15), Elderly (16); • Number of relevant events: 34, of which 25 serious, 9 non-serious; • Reported relevant PTs: Vasculitis (14), Cutaneous vasculitis and Vasculitic rash (4 each), (3), Giant cell arteritis and Peripheral ischaemia (3 each), Behcet's syndrome and Hypersensitivity vasculitis (2 each) Palpable purpura, and Takayasu's arteritis (1 each); • Relevant event onset latency (n = 25): Range from <24 hours to 19 days, median 3 days; • Relevant event outcome: fatal (1), resolved/resolving (13), not resolved (12) and unknown (8). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>

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Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
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- a. For the complete list of the AESIs, please refer to Appendix 5;
- b. Please note that this corresponds to evidence from post-EUA/conditional marketing authorisation approval data sources;
- c. Subjects with age ranged between 18 and 64 years;
- d. Subjects with age equal to or above 65 years;
- e. Subjects with age ranged between 2 and 11 years;
- f. Subjects with age ranged between 12 and less than 18 years;
- g. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events;
- h. Subjects with age ranged between 1 (28 days) and 23 months;
- i. Twenty-four additional cases were excluded from the analysis as they were not cases of peripheral facial nerve palsy because they described other disorders (stroke, cerebral haemorrhage or transient ischaemic attack); 1 case was excluded from the analysis because it was invalid due to an unidentifiable reporter;
- j. This UK case report received from the UK MHRA described a 1-year-old subject who received the vaccine, and had left postauricular ear pain that progressed to left-sided Bell’s palsy 1 day following vaccination that had not resolved at the time of the report;
- k. If a case included both PT Facial paresis and PT Facial paralysis, only the PT Facial paralysis was considered in the descriptions of the events as it is most clinically important;
- l. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events
- m. This UK case report received from the UK MHRA described a 7-year-old female subject who received the vaccine and had stroke (unknown outcome); no follow-up is possible for clarification.
- n. This PT not included in the AESIs/TME list was included in the review as relevant for ACCESS protocol criteria;

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3.1.4. Medication error

Cases potentially indicative of medication errors¹ that cumulatively occurred are summarized below.

- Number of relevant medication error cases: 2056² (4.9%) of which 1569 (3.7%) are medically confirmed.
- Number of relevant events: 2792
- Top 10 countries of incidence:
 - US (1201), France (171), UK (138), Germany (88), Czech Republic (87), Sweden (49), Israel (45), Italy (42), Canada (35), Romania (33), Finland (21), Portugal (20), Norway (14), Puerto Rico (13), Poland (12), Austria and Spain (10 each).

Medication error case outcomes:

- Fatal (7)³,
- Recovered/recovering (354, of which 4 are serious),
- Recovered with sequelae (8, of which 3 serious)

¹ MedDRA (version 23.1) Higher Level Terms: Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR Preferred Terms: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

² Thirty-five (35) cases were excluded from the analysis because describing medication errors occurring in an unspecified number of individuals or describing medication errors occurring with co suspects were determined to be non-contributory.

³ All the medication errors reported in these cases were assessed as non-serious occurrences with an unknown outcome; based on the available information including the causes of death, the relationship between the medication error and the death is weak. .

- Not recovered (189, of which 84 are serious),
- Unknown (1498, of which 33 are serious).

1371 cases reported only MEs without any associated clinical adverse event. The PTs most frequently reported (≥ 12 occurrences) were: Poor quality product administered (539), Product temperature excursion issue (253), Inappropriate schedule of product administration (225), Product preparation error (206), Underdose (202), Circumstance or information capable of leading to medication error (120), Product preparation issue (119), Wrong technique in product usage process (76), Incorrect route of product administration (66), Accidental overdose (33), Product administered at inappropriate site (27), Incorrect dose administered and Accidental exposure to the product (25 each), Exposure via skin contact (22), Wrong product administered (17), Incomplete course of vaccination, and Product administration error (14 each) Product administered to patient of inappropriate age (12).

In 685 cases, there were co-reported AEs. The most frequently co-associated AEs (> 40 occurrences) were: Headache (187), Pyrexia (161), Fatigue (135), Chills (127), Pain (107), Vaccination site pain (100), Nausea (89), Myalgia (88), Pain in extremity (85) Arthralgia (68), Off label use (57), Dizziness (52), Lymphadenopathy (47), Asthenia (46) and Malaise (41). These cases are summarized in Table 8.

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Accidental exposure to product	0	0	0	5
Accidental overdose	4	1	9	6
Booster dose missed	0	0	0	1
Circumstance or information capable of leading to medication error	0	0	5	11
Contraindicated product administered	1	0	0	2
Expired product administered	0	0	0	2
Exposure via skin contact	0	0	0	5
Inappropriate schedule of product administration	0	2	8	264
Incorrect dose administered	1	1	0	0

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Incorrect route of product administration	2	6	16	127
Lack of vaccination site rotation	1	0	0	0
Medication error	0	0	0	1
Poor quality product administered	1	0	0	34
Product administered at inappropriate site	2	1	13	29
Product administered to patient of inappropriate age	0	4	0	40
Product administration error	1	0	0	3
Product dose omission issue	0	1	0	3
Product preparation error	1	0	4	11
Product preparation issue	1	1	0	14

Overall, there were 68 cases with co-reported AEs reporting Harm and 599 cases with co-reported AEs without harm. Additionally, Intercepted medication errors was reported in 1 case (PTs Malaise, clinical outcome unknow) and Potential medication errors were reported in 17 cases.

4. DISCUSSION

Pfizer performs frequent and rigorous signal detection on BNT162b2 cases. The findings of these signal detection analyses are consistent with the known safety profile of the vaccine. This cumulative analysis to support the Biologics License Application for BNT162b2, is an integrated analysis of post-authorization safety data, from U.S. and foreign experience, focused on Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in the Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). The data do not reveal any novel safety concerns or risks requiring label changes and support a favorable benefit risk profile of to the BNT162b2 vaccine.

5. SUMMARY AND CONCLUSION

Review of the available data for this cumulative PM experience, confirms a favorable benefit: risk balance for BNT162b2.

Pfizer will continue routine pharmacovigilance activities on behalf of BioNTech according to the Pharmacovigilance Agreement in place, in order to assure patient safety and will inform the Agency if an evaluation of the safety data yields significant new information for BNT162b2.

APPENDIX 1. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

1p36 deletion syndrome;2-Hydroxyglutaric aciduria;5'nucleotidase increased;Acoustic neuritis;Acquired C1 inhibitor deficiency;Acquired epidermolysis bullosa;Acquired epileptic aphasia;Acute cutaneous lupus erythematosus;Acute disseminated encephalomyelitis;Acute encephalitis with refractory, repetitive partial seizures;Acute febrile neutrophilic dermatosis;Acute flaccid myelitis;Acute haemorrhagic leukoencephalitis;Acute haemorrhagic oedema of infancy;Acute kidney injury;Acute macular outer retinopathy;Acute motor axonal neuropathy;Acute motor-sensory axonal neuropathy;Acute myocardial infarction;Acute respiratory distress syndrome;Acute respiratory failure;Addison's disease;Administration site thrombosis;Administration site vasculitis;Adrenal thrombosis;Adverse event following immunisation;Ageusia;Agranulocytosis;Air embolism;Alanine aminotransferase abnormal;Alanine aminotransferase increased;Alcoholic seizure;Allergic bronchopulmonary mycosis;Allergic oedema;Alloimmune hepatitis;Alopecia areata;Alpers disease;Alveolar proteinosis;Ammonia abnormal;Ammonia increased;Amniotic cavity infection;Amygdalohippocampectomy;Amyloid arthropathy;Amyloidosis;Amyloidosis senile;Anaphylactic reaction;Anaphylactic shock;Anaphylactic transfusion reaction;Anaphylactoid reaction;Anaphylactoid shock;Anaphylactoid syndrome of pregnancy;Angioedema;Angiopathic neuropathy;Ankylosing spondylitis;Anosmia;Anti-acetylcholine receptor antibody positive;Anti-actin antibody positive;Anti-aquaporin-4 antibody positive;Anti-basal ganglia antibody positive;Anti-cyclic citrullinated peptide antibody positive;Anti-epithelial antibody positive;Anti-erythrocyte antibody positive;Anti-exosome complex antibody positive;Anti-GAD antibody negative;Anti-GAD antibody positive;Anti-ganglioside antibody positive;Antigliadin antibody positive;Anti-glomerular basement membrane antibody positive;Anti-glomerular basement membrane disease;Anti-glycyl-tRNA synthetase antibody positive;Anti-HLA antibody test positive;Anti-IA2 antibody positive;Anti-insulin antibody increased;Anti-insulin antibody positive;Anti-insulin receptor antibody increased;Anti-insulin receptor antibody positive;Anti-interferon antibody negative;Anti-interferon antibody positive;Anti-islet cell antibody positive;Antimitochondrial antibody positive;Anti-muscle specific kinase antibody positive;Anti-myelin-associated glycoprotein antibodies positive;Anti-myelin-associated glycoprotein associated polyneuropathy;Antimyocardial antibody positive;Anti-neuronal antibody positive;Antineutrophil cytoplasmic antibody increased;Antineutrophil cytoplasmic antibody positive;Anti-neutrophil cytoplasmic antibody positive vasculitis;Anti-NMDA antibody positive;Antinuclear antibody increased;Antinuclear antibody positive;Antiphospholipid antibodies positive;Antiphospholipid syndrome;Anti-platelet antibody positive;Anti-prothrombin antibody positive;Antiribosomal P antibody positive;Anti-RNA polymerase III antibody positive;Anti-saccharomyces cerevisiae antibody test positive;Anti-sperm antibody positive;Anti-SRP antibody positive;Antisynthetase syndrome;Anti-thyroid antibody positive;Anti-transglutaminase antibody increased;Anti-VGCC antibody positive;Anti-VGKC antibody positive;Anti-vimentin antibody positive;Antiviral prophylaxis;Antiviral treatment;Anti-zinc transporter 8 antibody positive;Aortic embolus;Aortic thrombosis;Aortitis;Aplasia pure red cell;Aplastic anaemia;Application site thrombosis;Application site vasculitis;Arrhythmia;Arterial bypass occlusion;Arterial bypass thrombosis;Arterial thrombosis;Arteriovenous fistula thrombosis;Arteriovenous graft site stenosis;Arteriovenous graft thrombosis;Arteritis;Arteritis

coronary;Arthralgia;Arthritis;Arthritis enteropathic;Ascites;Aseptic cavernous sinus thrombosis;Aspartate aminotransferase abnormal;Aspartate aminotransferase increased;Aspartate-glutamate-transporter deficiency;AST to platelet ratio index increased;AST/ALT ratio abnormal;Asthma;Asymptomatic COVID-19;Ataxia;Atheroembolism;Atonic seizures;Atrial thrombosis;Atrophic thyroiditis;Atypical benign partial epilepsy;Atypical pneumonia;Aura;Autoantibody positive;Autoimmune anaemia;Autoimmune aplastic anaemia;Autoimmune arthritis;Autoimmune blistering disease;Autoimmune cholangitis;Autoimmune colitis;Autoimmune demyelinating disease;Autoimmune dermatitis;Autoimmune disorder;Autoimmune encephalopathy;Autoimmune endocrine disorder;Autoimmune enteropathy;Autoimmune eye disorder;Autoimmune haemolytic anaemia;Autoimmune heparin-induced thrombocytopenia;Autoimmune hepatitis;Autoimmune hyperlipidaemia;Autoimmune hypothyroidism;Autoimmune inner ear disease;Autoimmune lung disease;Autoimmune lymphoproliferative syndrome;Autoimmune myocarditis;Autoimmune myositis;Autoimmune nephritis;Autoimmune neuropathy;Autoimmune neutropenia;Autoimmune pancreatitis;Autoimmune pancytopenia;Autoimmune pericarditis;Autoimmune retinopathy;Autoimmune thyroid disorder;Autoimmune thyroiditis;Autoimmune uveitis;Autoinflammation with infantile enterocolitis;Autoinflammatory disease;Automatism epileptic;Autonomic nervous system imbalance;Autonomic seizure;Axial spondyloarthritis;Axillary vein thrombosis;Axonal and demyelinating polyneuropathy;Axonal neuropathy;Bacterascites;Baltic myoclonic epilepsy;Band sensation;Basedow's disease;Basilar artery thrombosis;Basophilopenia;B-cell aplasia;Behcet's syndrome;Benign ethnic neutropenia;Benign familial neonatal convulsions;Benign familial pemphigus;Benign rolandic epilepsy;Beta-2 glycoprotein antibody positive;Bickerstaff's encephalitis;Bile output abnormal;Bile output decreased;Biliary ascites;Bilirubin conjugated abnormal;Bilirubin conjugated increased;Bilirubin urine present;Biopsy liver abnormal;Biotinidase deficiency;Birdshot chorioretinopathy;Blood alkaline phosphatase abnormal;Blood alkaline phosphatase increased;Blood bilirubin abnormal;Blood bilirubin increased;Blood bilirubin unconjugated increased;Blood cholinesterase abnormal;Blood cholinesterase decreased;Blood pressure decreased;Blood pressure diastolic decreased;Blood pressure systolic decreased;Blue toe syndrome;Brachiocephalic vein thrombosis;Brain stem embolism;Brain stem thrombosis;Bromosulphthalein test abnormal;Bronchial oedema;Bronchitis;Bronchitis mycoplasmal;Bronchitis viral;Bronchopulmonary aspergillosis allergic;Bronchospasm;Budd-Chiari syndrome;Bulbar palsy;Butterfly rash;C1q nephropathy;Caesarean section;Calcium embolism;Capillaritis;Caplan's syndrome;Cardiac amyloidosis;Cardiac arrest;Cardiac failure;Cardiac failure acute;Cardiac sarcoidosis;Cardiac ventricular thrombosis;Cardiogenic shock;Cardiolipin antibody positive;Cardiopulmonary failure;Cardio-respiratory arrest;Cardio-respiratory distress;Cardiovascular insufficiency;Carotid arterial embolus;Carotid artery thrombosis;Cataplexy;Catheter site thrombosis;Catheter site vasculitis;Cavernous sinus thrombosis;CDKL5 deficiency disorder;CEC syndrome;Cement embolism;Central nervous system lupus;Central nervous system vasculitis;Cerebellar artery thrombosis;Cerebellar embolism;Cerebral amyloid angiopathy;Cerebral arteritis;Cerebral artery embolism;Cerebral artery thrombosis;Cerebral gas embolism;Cerebral microembolism;Cerebral septic infarct;Cerebral thrombosis;Cerebral venous sinus thrombosis;Cerebral venous thrombosis;Cerebrospinal thrombotic

tamponade;Cerebrovascular accident;Change in seizure presentation;Chest discomfort;Child-Pugh-Turcotte score abnormal;Child-Pugh-Turcotte score increased;Chillblains;Choking;Choking sensation;Cholangitis sclerosing;Chronic autoimmune glomerulonephritis;Chronic cutaneous lupus erythematosus;Chronic fatigue syndrome;Chronic gastritis;Chronic inflammatory demyelinating polyradiculoneuropathy;Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids;Chronic recurrent multifocal osteomyelitis;Chronic respiratory failure;Chronic spontaneous urticaria;Circulatory collapse;Circumoral oedema;Circumoral swelling;Clinically isolated syndrome;Clonic convulsion;Coeliac disease;Cogan's syndrome;Cold agglutinins positive;Cold type haemolytic anaemia;Colitis;Colitis erosive;Colitis herpes;Colitis microscopic;Colitis ulcerative;Collagen disorder;Collagen-vascular disease;Complement factor abnormal;Complement factor C1 decreased;Complement factor C2 decreased;Complement factor C3 decreased;Complement factor C4 decreased;Complement factor decreased;Computerised tomogram liver abnormal;Concentric sclerosis;Congenital anomaly;Congenital bilateral perisylvian syndrome;Congenital herpes simplex infection;Congenital myasthenic syndrome;Congenital varicella infection;Congestive hepatopathy;Convulsion in childhood;Convulsions local;Convulsive threshold lowered;Coombs positive haemolytic anaemia;Coronary artery disease;Coronary artery embolism;Coronary artery thrombosis;Coronary bypass thrombosis;Coronavirus infection;Coronavirus test;Coronavirus test negative;Coronavirus test positive;Corpus callosotomy;Cough;Cough variant asthma;COVID-19;COVID-19 immunisation;COVID-19 pneumonia;COVID-19 prophylaxis;COVID-19 treatment;Cranial nerve disorder;Cranial nerve palsies multiple;Cranial nerve paralysis;CREST syndrome;Crohn's disease;Cryofibrinogenaemia;Cryoglobulinaemia;CSF oligoclonal band present;CSWS syndrome;Cutaneous amyloidosis;Cutaneous lupus erythematosus;Cutaneous sarcoidosis;Cutaneous vasculitis;Cyanosis;Cyclic neutropenia;Cystitis interstitial;Cytokine release syndrome;Cytokine storm;De novo purine synthesis inhibitors associated acute inflammatory syndrome;Death neonatal;Deep vein thrombosis;Deep vein thrombosis postoperative;Deficiency of bile secretion;Deja vu;Demyelinating polyneuropathy;Demyelination;Dermatitis;Dermatitis bullous;Dermatitis herpetiformis;Dermatomyositis;Device embolisation;Device related thrombosis;Diabetes mellitus;Diabetic ketoacidosis;Diabetic mastopathy;Dialysis amyloidosis;Dialysis membrane reaction;Diastolic hypotension;Diffuse vasculitis;Digital pitting scar;Disseminated intravascular coagulation;Disseminated intravascular coagulation in newborn;Disseminated neonatal herpes simplex;Disseminated varicella;Disseminated varicella zoster vaccine virus infection;Disseminated varicella zoster virus infection;DNA antibody positive;Double cortex syndrome;Double stranded DNA antibody positive;Dreamy state;Dressler's syndrome;Drop attacks;Drug withdrawal convulsions;Dyspnoea;Early infantile epileptic encephalopathy with burst-suppression;Eclampsia;Eczema herpeticum;Embolia cutis medicamentosa;Embolic cerebellar infarction;Embolic cerebral infarction;Embolic pneumonia;Embolic stroke;Embolism;Embolism arterial;Embolism venous;Encephalitis;Encephalitis allergic;Encephalitis autoimmune;Encephalitis brain stem;Encephalitis haemorrhagic;Encephalitis periaxialis diffusa;Encephalitis post immunisation;Encephalomyelitis;Encephalopathy;Endocrine disorder;Endocrine ophthalmopathy;Endotracheal intubation;Enteritis;Enteritis leukopenic;Enterobacter pneumonia;Enterocolitis;Enteropathic spondylitis;Eosinopenia;Eosinophilic

fasciitis;Eosinophilic granulomatosis with polyangiitis;Eosinophilic oesophagitis;Epidermolysis;Epilepsy;Epilepsy surgery;Epilepsy with myoclonic-atonic seizures;Epileptic aura;Epileptic psychosis;Erythema;Erythema induratum;Erythema multiforme;Erythema nodosum;Evans syndrome;Exanthema subitum;Expanded disability status scale score decreased;Expanded disability status scale score increased;Exposure to communicable disease;Exposure to SARS-CoV-2;Eye oedema;Eye pruritus;Eye swelling;Eyelid oedema;Face oedema;Facial paralysis;Facial paresis;Faciobrachial dystonic seizure;Fat embolism;Febrile convulsion;Febrile infection-related epilepsy syndrome;Febrile neutropenia;Felty's syndrome;Femoral artery embolism;Fibrillary glomerulonephritis;Fibromyalgia;Flushing;Foaming at mouth;Focal cortical resection;Focal dyscognitive seizures;Foetal distress syndrome;Foetal placental thrombosis;Foetor hepaticus;Foreign body embolism;Frontal lobe epilepsy;Fulminant type 1 diabetes mellitus;Galactose elimination capacity test abnormal;Galactose elimination capacity test decreased;Gamma-glutamyltransferase abnormal;Gamma-glutamyltransferase increased;Gastritis herpes;Gastrointestinal amyloidosis;Gelastic seizure;Generalised onset non-motor seizure;Generalised tonic-clonic seizure;Genital herpes;Genital herpes simplex;Genital herpes zoster;Giant cell arteritis;Glomerulonephritis;Glomerulonephritis membranoproliferative;Glomerulonephritis membranous;Glomerulonephritis rapidly progressive;Glossopharyngeal nerve paralysis;Glucose transporter type 1 deficiency syndrome;Glutamate dehydrogenase increased;Glycocholic acid increased;GM2 gangliosidosis;Goodpasture's syndrome;Graft thrombosis;Granulocytopenia;Granulocytopenia neonatal;Granulomatosis with polyangiitis;Granulomatous dermatitis;Grey matter heterotopia;Guanase increased;Guillain-Barre syndrome;Haemolytic anaemia;Haemophagocytic lymphohistiocytosis;Haemorrhage;Haemorrhagic ascites;Haemorrhagic disorder;Haemorrhagic pneumonia;Haemorrhagic varicella syndrome;Haemorrhagic vasculitis;Hantavirus pulmonary infection;Hashimoto's encephalopathy;Hashitoxicosis;Hemimegalencephaly;Henoch-Schonlein purpura;Henoch-Schonlein purpura nephritis;Hepaplastin abnormal;Hepaplastin decreased;Heparin-induced thrombocytopenia;Hepatic amyloidosis;Hepatic artery embolism;Hepatic artery flow decreased;Hepatic artery thrombosis;Hepatic enzyme abnormal;Hepatic enzyme decreased;Hepatic enzyme increased;Hepatic fibrosis marker abnormal;Hepatic fibrosis marker increased;Hepatic function abnormal;Hepatic hydrothorax;Hepatic hypertrophy;Hepatic hypoperfusion;Hepatic lymphocytic infiltration;Hepatic mass;Hepatic pain;Hepatic sequestration;Hepatic vascular resistance increased;Hepatic vascular thrombosis;Hepatic vein embolism;Hepatic vein thrombosis;Hepatic venous pressure gradient abnormal;Hepatic venous pressure gradient increased;Hepatitis;Hepatobiliary scan abnormal;Hepatomegaly;Hepatosplenomegaly;Hereditary angioedema with C1 esterase inhibitor deficiency;Herpes dermatitis;Herpes gestationis;Herpes oesophagitis;Herpes ophthalmic;Herpes pharyngitis;Herpes sepsis;Herpes simplex;Herpes simplex cervicitis;Herpes simplex colitis;Herpes simplex encephalitis;Herpes simplex gastritis;Herpes simplex hepatitis;Herpes simplex meningitis;Herpes simplex meningoencephalitis;Herpes simplex meningomyelitis;Herpes simplex necrotising retinopathy;Herpes simplex oesophagitis;Herpes simplex otitis externa;Herpes simplex pharyngitis;Herpes simplex pneumonia;Herpes simplex reactivation;Herpes simplex sepsis;Herpes simplex viraemia;Herpes simplex virus conjunctivitis neonatal;Herpes simplex visceral;Herpes virus

infection;Herpes zoster;Herpes zoster cutaneous disseminated;Herpes zoster infection neurological;Herpes zoster meningitis;Herpes zoster meningoencephalitis;Herpes zoster meningomyelitis;Herpes zoster meningoradiculitis;Herpes zoster necrotising retinopathy;Herpes zoster oticus;Herpes zoster pharyngitis;Herpes zoster reactivation;Herpetic radiculopathy;Histone antibody positive;Hoigne's syndrome;Human herpesvirus 6 encephalitis;Human herpesvirus 6 infection;Human herpesvirus 6 infection reactivation;Human herpesvirus 7 infection;Human herpesvirus 8 infection;Hyperammonaemia;Hyperbilirubinaemia;Hypercholia;Hypergammaglobulinaemia benign monoclonal;Hyperglycaemic seizure;Hypersensitivity;Hypersensitivity vasculitis;Hyperthyroidism;Hypertransaminaemia;Hyperventilation;Hypoalbuminaemia;Hypocalcaemic seizure;Hypogammaglobulinaemia;Hypoglossal nerve paralysis;Hypoglossal nerve paresis;Hypoglycaemic seizure;Hyponatraemic seizure;Hypotension;Hypotensive crisis;Hypothenar hammer syndrome;Hypothyroidism;Hypoxia;Idiopathic CD4 lymphocytopenia;Idiopathic generalised epilepsy;Idiopathic interstitial pneumonia;Idiopathic neutropenia;Idiopathic pulmonary fibrosis;IgA nephropathy;IgM nephropathy;IIIrd nerve paralysis;IIIrd nerve paresis;Iliac artery embolism;Immune thrombocytopenia;Immune-mediated adverse reaction;Immune-mediated cholangitis;Immune-mediated cholestasis;Immune-mediated cytopenia;Immune-mediated encephalitis;Immune-mediated encephalopathy;Immune-mediated endocrinopathy;Immune-mediated enterocolitis;Immune-mediated gastritis;Immune-mediated hepatic disorder;Immune-mediated hepatitis;Immune-mediated hyperthyroidism;Immune-mediated hypothyroidism;Immune-mediated myocarditis;Immune-mediated myositis;Immune-mediated nephritis;Immune-mediated neuropathy;Immune-mediated pancreatitis;Immune-mediated pneumonitis;Immune-mediated renal disorder;Immune-mediated thyroiditis;Immune-mediated uveitis;Immunoglobulin G4 related disease;Immunoglobulins abnormal;Implant site thrombosis;Inclusion body myositis;Infantile genetic agranulocytosis;Infantile spasms;Infected vasculitis;Infective thrombosis;Inflammation;Inflammatory bowel disease;Infusion site thrombosis;Infusion site vasculitis;Injection site thrombosis;Injection site urticaria;Injection site vasculitis;Instillation site thrombosis;Insulin autoimmune syndrome;Interstitial granulomatous dermatitis;Interstitial lung disease;Intracardiac mass;Intracardiac thrombus;Intracranial pressure increased;Intrapericardial thrombosis;Intrinsic factor antibody abnormal;Intrinsic factor antibody positive;IPEX syndrome;Irregular breathing;IRVAN syndrome;IVth nerve paralysis;IVth nerve paresis;JC polyomavirus test positive;JC virus CSF test positive;Jeavons syndrome;Jugular vein embolism;Jugular vein thrombosis;Juvenile idiopathic arthritis;Juvenile myoclonic epilepsy;Juvenile polymyositis;Juvenile psoriatic arthritis;Juvenile spondyloarthritis;Kaposi sarcoma inflammatory cytokine syndrome;Kawasaki's disease;Kayser-Fleischer ring;Keratoderma blenorrhagica;Ketosis-prone diabetes mellitus;Kounis syndrome;Lafora's myoclonic epilepsy;Lamb's excrescences;Laryngeal dyspnoea;Laryngeal oedema;Laryngeal rheumatoid arthritis;Laryngospasm;Laryngotracheal oedema;Latent autoimmune diabetes in adults;LE cells present;Lemierre syndrome;Lennox-Gastaut syndrome;Leucine aminopeptidase increased;Leukoencephalomyelitis;Leukoencephalopathy;Leukopenia;Leukopenia neonatal;Lewis-Sumner syndrome;Lhermitte's sign;Lichen planopilaris;Lichen planus;Lichen sclerosus;Limbic encephalitis;Linear IgA disease;Lip oedema;Lip swelling;Liver function test abnormal;Liver function test decreased;Liver function test increased;Liver induration;Liver injury;Liver iron concentration abnormal;Liver iron concentration

increased;Liver opacity;Liver palpable;Liver sarcoidosis;Liver scan abnormal;Liver tenderness;Low birth weight baby;Lower respiratory tract herpes infection;Lower respiratory tract infection;Lower respiratory tract infection viral;Lung abscess;Lupoid hepatic cirrhosis;Lupus cystitis;Lupus encephalitis;Lupus endocarditis;Lupus enteritis;Lupus hepatitis;Lupus myocarditis;Lupus myositis;Lupus nephritis;Lupus pancreatitis;Lupus pleurisy;Lupus pneumonitis;Lupus vasculitis;Lupus-like syndrome;Lymphocytic hypophysitis;Lymphocytopenia neonatal;Lymphopenia;MAGIC syndrome;Magnetic resonance imaging liver abnormal;Magnetic resonance proton density fat fraction measurement;Mahler sign;Manufacturing laboratory analytical testing issue;Manufacturing materials issue;Manufacturing production issue;Marburg's variant multiple sclerosis;Marchiafava-Bignami disease;Marine Lenhart syndrome;Mastocytic enterocolitis;Maternal exposure during pregnancy;Medical device site thrombosis;Medical device site vasculitis;MELAS syndrome;Meningitis;Meningitis aseptic;Meningitis herpes;Meningoencephalitis herpes simplex neonatal;Meningoencephalitis herpetic;Meningomyelitis herpes;MERS-CoV test;MERS-CoV test negative;MERS-CoV test positive;Mesangioproliferative glomerulonephritis;Mesenteric artery embolism;Mesenteric artery thrombosis;Mesenteric vein thrombosis;Metapneumovirus infection;Metastatic cutaneous Crohn's disease;Metastatic pulmonary embolism;Microangiopathy;Microembolism;Microscopic polyangiitis;Middle East respiratory syndrome;Migraine-triggered seizure;Miliary pneumonia;Miller Fisher syndrome;Mitochondrial aspartate aminotransferase increased;Mixed connective tissue disease;Model for end stage liver disease score abnormal;Model for end stage liver disease score increased;Molar ratio of total branched-chain amino acid to tyrosine;Molybdenum cofactor deficiency;Monocytopenia;Mononeuritis;Mononeuropathy multiplex;Morphaea;Morvan syndrome;Mouth swelling;Moyamoya disease;Multifocal motor neuropathy;Multiple organ dysfunction syndrome;Multiple sclerosis;Multiple sclerosis relapse;Multiple sclerosis relapse prophylaxis;Multiple subpial transection;Multisystem inflammatory syndrome in children;Muscular sarcoidosis;Myasthenia gravis;Myasthenia gravis crisis;Myasthenia gravis neonatal;Myasthenic syndrome;Myelitis;Myelitis transverse;Myocardial infarction;Myocarditis;Myocarditis post infection;Myoclonic epilepsy;Myoclonic epilepsy and ragged-red fibres;Myokymia;Myositis;Narcolepsy;Nasal herpes;Nasal obstruction;Necrotising herpetic retinopathy;Neonatal Crohn's disease;Neonatal epileptic seizure;Neonatal lupus erythematosus;Neonatal mucocutaneous herpes simplex;Neonatal pneumonia;Neonatal seizure;Nephritis;Nephrogenic systemic fibrosis;Neuralgic amyotrophy;Neuritis;Neuritis cranial;Neuromyelitis optica pseudo relapse;Neuromyelitis optica spectrum disorder;Neuromyotonia;Neuronal neuropathy;Neuropathy peripheral;Neuropathy, ataxia, retinitis pigmentosa syndrome;Neuropsychiatric lupus;Neurosarcoidosis;Neutropenia;Neutropenia neonatal;Neutropenic colitis;Neutropenic infection;Neutropenic sepsis;Nodular rash;Nodular vasculitis;Noninfectious myelitis;Noninfective encephalitis;Noninfective encephalomyelitis;Noninfective oophoritis;Obstetrical pulmonary embolism;Occupational exposure to communicable disease;Occupational exposure to SARS-CoV-2;Ocular hyperaemia;Ocular myasthenia;Ocular pemphigoid;Ocular sarcoidosis;Ocular vasculitis;Oculofacial paralysis;Oedema;Oedema blister;Oedema due to hepatic disease;Oedema mouth;Oesophageal achalasia;Ophthalmic artery thrombosis;Ophthalmic herpes simplex;Ophthalmic herpes zoster;Ophthalmic vein thrombosis;Optic neuritis;Optic

neuropathy;Optic perineuritis;Oral herpes;Oral lichen planus;Oropharyngeal oedema;Oropharyngeal spasm;Oropharyngeal swelling;Osmotic demyelination syndrome;Ovarian vein thrombosis;Overlap syndrome;Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection;Paget-Schroetter syndrome;Palindromic rheumatism;Palisaded neutrophilic granulomatous dermatitis;Palmoplantar keratoderma;Palpable purpura;Pancreatitis;Panencephalitis;Papillophlebitis;Paracancerous pneumonia;Paradoxical embolism;Parainfluenzae viral laryngotracheobronchitis;Paraneoplastic dermatomyositis;Paraneoplastic pemphigus;Paraneoplastic thrombosis;Paresis cranial nerve;Parietal cell antibody positive;Paroxysmal nocturnal haemoglobinuria;Partial seizures;Partial seizures with secondary generalisation;Patient isolation;Pelvic venous thrombosis;Pemphigoid;Pemphigus;Penile vein thrombosis;Pericarditis;Pericarditis lupus;Perihepatic discomfort;Periorbital oedema;Periorbital swelling;Peripheral artery thrombosis;Peripheral embolism;Peripheral ischaemia;Peripheral vein thrombus extension;Periportal oedema;Peritoneal fluid protein abnormal;Peritoneal fluid protein decreased;Peritoneal fluid protein increased;Peritonitis lupus;Pernicious anaemia;Petit mal epilepsy;Pharyngeal oedema;Pharyngeal swelling;Pityriasis lichenoides et varioliformis acuta;Placenta praevia;Pleuroparenchymal fibroelastosis;Pneumobilia;Pneumonia;Pneumonia adenoviral;Pneumonia cytomegaloviral;Pneumonia herpes viral;Pneumonia influenzal;Pneumonia measles;Pneumonia mycoplasmal;Pneumonia necrotising;Pneumonia parainfluenzae viral;Pneumonia respiratory syncytial viral;Pneumonia viral;POEMS syndrome;Polyarteritis nodosa;Polyarthritis;Polychondritis;Polyglandular autoimmune syndrome type I;Polyglandular autoimmune syndrome type II;Polyglandular autoimmune syndrome type III;Polyglandular disorder;Polymicrogyria;Polymyalgia rheumatica;Polymyositis;Polyneuropathy;Polyneuropathy idiopathic progressive;Portal pyaemia;Portal vein embolism;Portal vein flow decreased;Portal vein pressure increased;Portal vein thrombosis;Portosplenomesenteric venous thrombosis;Post procedural hypotension;Post procedural pneumonia;Post procedural pulmonary embolism;Post stroke epilepsy;Post stroke seizure;Post thrombotic retinopathy;Post thrombotic syndrome;Post viral fatigue syndrome;Postictal headache;Postictal paralysis;Postictal psychosis;Postictal state;Postoperative respiratory distress;Postoperative respiratory failure;Postoperative thrombosis;Postpartum thrombosis;Postpartum venous thrombosis;Postpericardiotomy syndrome;Post-traumatic epilepsy;Postural orthostatic tachycardia syndrome;Precerebral artery thrombosis;Pre-eclampsia;Preictal state;Premature labour;Premature menopause;Primary amyloidosis;Primary biliary cholangitis;Primary progressive multiple sclerosis;Procedural shock;Proctitis herpes;Proctitis ulcerative;Product availability issue;Product distribution issue;Product supply issue;Progressive facial hemiatrophy;Progressive multifocal leukoencephalopathy;Progressive multiple sclerosis;Progressive relapsing multiple sclerosis;Prosthetic cardiac valve thrombosis;Pruritus;Pruritus allergic;Pseudovasculitis;Psoriasis;Psoriatic arthropathy;Pulmonary amyloidosis;Pulmonary artery thrombosis;Pulmonary embolism;Pulmonary fibrosis;Pulmonary haemorrhage;Pulmonary microemboli;Pulmonary oil microembolism;Pulmonary renal syndrome;Pulmonary sarcoidosis;Pulmonary sepsis;Pulmonary thrombosis;Pulmonary tumour thrombotic microangiopathy;Pulmonary vasculitis;Pulmonary veno-occlusive disease;Pulmonary venous thrombosis;Pyoderma gangrenosum;Pyostomatitis vegetans;Pyrexia;Quarantine;Radiation leukopenia;Radiculitis

brachial;Radiologically isolated syndrome;Rash;Rash erythematous;Rash pruritic;Rasmussen encephalitis;Raynaud's phenomenon;Reactive capillary endothelial proliferation;Relapsing multiple sclerosis;Relapsing-remitting multiple sclerosis;Renal amyloidosis;Renal arteritis;Renal artery thrombosis;Renal embolism;Renal failure;Renal vascular thrombosis;Renal vasculitis;Renal vein embolism;Renal vein thrombosis;Respiratory arrest;Respiratory disorder;Respiratory distress;Respiratory failure;Respiratory paralysis;Respiratory syncytial virus bronchiolitis;Respiratory syncytial virus bronchitis;Retinal artery embolism;Retinal artery occlusion;Retinal artery thrombosis;Retinal vascular thrombosis;Retinal vasculitis;Retinal vein occlusion;Retinal vein thrombosis;Retinol binding protein decreased;Retinopathy;Retrograde portal vein flow;Retroperitoneal fibrosis;Reversible airways obstruction;Reynold's syndrome;Rheumatic brain disease;Rheumatic disorder;Rheumatoid arthritis;Rheumatoid factor increased;Rheumatoid factor positive;Rheumatoid factor quantitative increased;Rheumatoid lung;Rheumatoid neutrophilic dermatosis;Rheumatoid nodule;Rheumatoid nodule removal;Rheumatoid scleritis;Rheumatoid vasculitis;Saccadic eye movement;SAPHO syndrome;Sarcoidosis;SARS-CoV-1 test;SARS-CoV-1 test negative;SARS-CoV-1 test positive;SARS-CoV-2 antibody test;SARS-CoV-2 antibody test negative;SARS-CoV-2 antibody test positive;SARS-CoV-2 carrier;SARS-CoV-2 sepsis;SARS-CoV-2 test;SARS-CoV-2 test false negative;SARS-CoV-2 test false positive;SARS-CoV-2 test negative;SARS-CoV-2 test positive;SARS-CoV-2 viraemia;Satoyoshi syndrome;Schizencephaly;Scleritis;Sclerodactylia;Scleroderma;Scleroderma associated digital ulcer;Scleroderma renal crisis;Scleroderma-like reaction;Secondary amyloidosis;Secondary cerebellar degeneration;Secondary progressive multiple sclerosis;Segmented hyalinising vasculitis;Seizure;Seizure anoxic;Seizure cluster;Seizure like phenomena;Seizure prophylaxis;Sensation of foreign body;Septic embolus;Septic pulmonary embolism;Severe acute respiratory syndrome;Severe myoclonic epilepsy of infancy;Shock;Shock symptom;Shrinking lung syndrome;Shunt thrombosis;Silent thyroiditis;Simple partial seizures;Sjogren's syndrome;Skin swelling;SLE arthritis;Smooth muscle antibody positive;Sneezing;Spinal artery embolism;Spinal artery thrombosis;Splenic artery thrombosis;Splenic embolism;Splenic thrombosis;Splenic vein thrombosis;Spondylitis;Spondyloarthropathy;Spontaneous heparin-induced thrombocytopenia syndrome;Status epilepticus;Stevens-Johnson syndrome;Stiff leg syndrome;Stiff person syndrome;Stillbirth;Still's disease;Stoma site thrombosis;Stoma site vasculitis;Stress cardiomyopathy;Stridor;Subacute cutaneous lupus erythematosus;Subacute endocarditis;Subacute inflammatory demyelinating polyneuropathy;Subclavian artery embolism;Subclavian artery thrombosis;Subclavian vein thrombosis;Sudden unexplained death in epilepsy;Superior sagittal sinus thrombosis;Susac's syndrome;Suspected COVID-19;Swelling;Swelling face;Swelling of eyelid;Swollen tongue;Sympathetic ophthalmia;Systemic lupus erythematosus;Systemic lupus erythematosus disease activity index abnormal;Systemic lupus erythematosus disease activity index decreased;Systemic lupus erythematosus disease activity index increased;Systemic lupus erythematosus rash;Systemic scleroderma;Systemic sclerosis pulmonary;Tachycardia;Tachypnoea;Takayasu's arteritis;Temporal lobe epilepsy;Terminal ileitis;Testicular autoimmunity;Throat tightness;Thromboangiitis obliterans;Thrombocytopenia;Thrombocytopenic purpura;Thrombophlebitis;Thrombophlebitis migrans;Thrombophlebitis

neonatal;Thrombophlebitis septic;Thrombophlebitis superficial;Thromboplastin antibody positive;Thrombosis;Thrombosis corpora cavernosa;Thrombosis in device;Thrombosis mesenteric vessel;Thrombotic cerebral infarction;Thrombotic microangiopathy;Thrombotic stroke;Thrombotic thrombocytopenic purpura;Thyroid disorder;Thyroid stimulating immunoglobulin increased;Thyroiditis;Tongue amyloidosis;Tongue biting;Tongue oedema;Tonic clonic movements;Tonic convulsion;Tonic posturing;Topectomy;Total bile acids increased;Toxic epidermal necrolysis;Toxic leukoencephalopathy;Toxic oil syndrome;Tracheal obstruction;Tracheal oedema;Tracheobronchitis;Tracheobronchitis mycoplasmal;Tracheobronchitis viral;Transaminases abnormal;Transaminases increased;Transfusion-related alloimmune neutropenia;Transient epileptic amnesia;Transverse sinus thrombosis;Trigeminal nerve paresis;Trigeminal neuralgia;Trigeminal palsy;Truncus coeliacus thrombosis;Tuberous sclerosis complex;Tubulointerstitial nephritis and uveitis syndrome;Tumefactive multiple sclerosis;Tumour embolism;Tumour thrombosis;Type 1 diabetes mellitus;Type I hypersensitivity;Type III immune complex mediated reaction;Uhthoff's phenomenon;Ulcerative keratitis;Ultrasound liver abnormal;Umbilical cord thrombosis;Uncinate fits;Undifferentiated connective tissue disease;Upper airway obstruction;Urine bilirubin increased;Urobilinogen urine decreased;Urobilinogen urine increased;Urticaria;Urticaria papular;Urticarial vasculitis;Uterine rupture;Uveitis;Vaccination site thrombosis;Vaccination site vasculitis;Vagus nerve paralysis;Varicella;Varicella keratitis;Varicella post vaccine;Varicella zoster gastritis;Varicella zoster oesophagitis;Varicella zoster pneumonia;Varicella zoster sepsis;Varicella zoster virus infection;Vasa praevia;Vascular graft thrombosis;Vascular pseudoaneurysm thrombosis;Vascular purpura;Vascular stent thrombosis;Vasculitic rash;Vasculitic ulcer;Vasculitis;Vasculitis gastrointestinal;Vasculitis necrotising;Vena cava embolism;Vena cava thrombosis;Venous intravasation;Venous recanalisation;Venous thrombosis;Venous thrombosis in pregnancy;Venous thrombosis limb;Venous thrombosis neonatal;Vertebral artery thrombosis;Vessel puncture site thrombosis;Visceral venous thrombosis;VIth nerve paralysis;VIth nerve paresis;Vitiligo;Vocal cord paralysis;Vocal cord paresis;Vogt-Koyanagi-Harada disease;Warm type haemolytic anaemia;Wheezing;White nipple sign;XIth nerve paralysis;X-ray hepatobiliary abnormal;Young's syndrome;Zika virus associated Guillain Barre syndrome.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

COMIRNATY® (COVID-19 Vaccine, mRNA) suspension for injection, for intramuscular use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE
 COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- COMIRNATY supplied in multiple dose vials with gray caps and labels with gray borders **MUST NOT** be diluted prior to use. (2.1)
- For intramuscular injection only. (2.2)
- COMIRNATY is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart. (2.3)

DOSAGE FORMS AND STRENGTHS
 Suspension for injection. A single dose is 0.3 mL. (3)

CONTRAINDICATIONS
 Known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY. (4)

WARNINGS AND PRECAUTIONS

- Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. (5.2)
- Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY. Procedures should be in place to avoid injury from fainting. (5.4)

ADVERSE REACTIONS

- In clinical studies of participants 16 through 55 years of age, the most commonly reported adverse reactions (≥10%) 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%). (6.1)
- In clinical studies of participants 56 years of age and older, the most commonly reported adverse reactions (≥10%) were pain at the injection site (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%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.
 See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

The storage, preparation, and administration information in this Prescribing Information apply to COMIRNATY for individuals 16 years of age and older supplied in multiple dose vials with gray caps and labels with gray borders, which **MUST NOT** be diluted prior to use.

COMIRNATY Multiple Dose Vial with Gray Cap and Label with a Gray Border

Age Range	Dilution Information	Doses Per Vial	Dose Volume
16 years and older	Do not dilute prior to use	6	0.3 mL

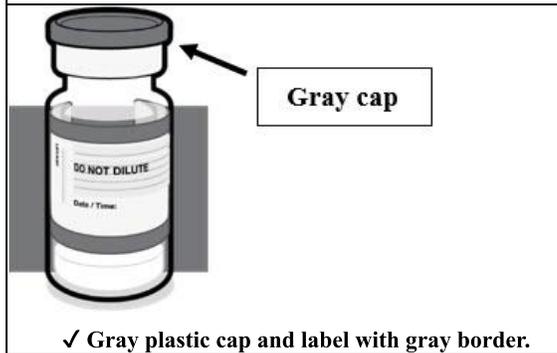
DO NOT DILUTE

- COMIRNATY multiple dose vial with a gray cap and a label with a gray border contains a volume of 2.25 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed prior to administration. **DO NOT DILUTE** prior to use.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] [*see How Supplied/Storage and Handling (16)*].

- Refer to thawing instructions in the panels below.
- One vial contains 6 doses of 0.3 mL.

Preparation Instructions

COMIRNATY Vial with Gray Cap and Label with Gray Border – Vial Verification

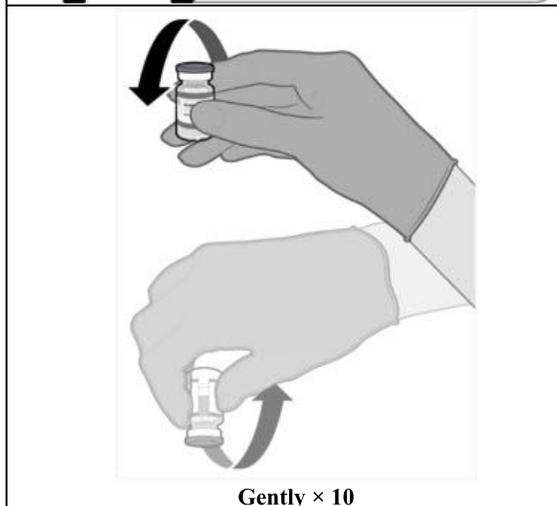


- Verify that the vial of COMIRNATY has a gray plastic cap and a label with a gray border.

COMIRNATY Vial with Gray Cap and Label with Gray Border – Thawing Prior to Use

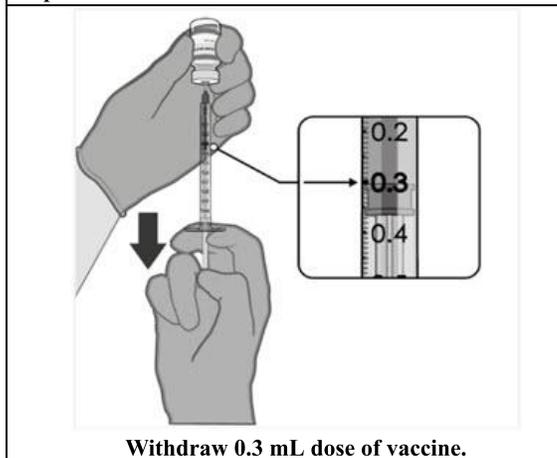


- Thaw vial(s) of COMIRNATY before use either by:
 - Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of 10 vials may take up to 6 hours to thaw, and thawed vials can be stored in the refrigerator for up to 10 weeks.
 - Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.
- Vials may be stored at room temperature [up to 25°C (77°F)] for up to 12 hours prior to use.



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

COMIRNATY Vial with Gray Cap and Label with Gray Border – Preparation of Individual 0.3 mL Doses



- Withdraw 0.3 mL of COMIRNATY preferentially using low dead-volume syringes and/or needles.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in a single vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Administer immediately.

Preparation Instructions

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

- Record the date and time of first vial puncture on the COMIRNATY vial label.
- Store between 2°C to 25°C (35°F to 77°F).
- Discard any unused vaccine 12 hours after first puncture.

Vials of COMIRNATY with gray caps and labels with gray borders contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses 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.

2.2 Administration Information

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

Administer a single 0.3 mL dose of COMIRNATY intramuscularly.

2.3 Vaccination Schedule

COMIRNATY is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart.

There are no data available on the interchangeability of COMIRNATY with COVID-19 vaccines from other manufacturers to complete the vaccination series. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

COMIRNATY is a suspension for injection. Each dose of COMIRNATY supplied in vials with gray caps and labels with gray borders is 0.3 mL.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS**5.1 Management of Acute Allergic Reactions**

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

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

5.3 Syncope

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

5.4 Altered Immunocompetence

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

5.5 Limitation of Effectiveness

COMIRNATY may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In clinical studies, the most commonly reported ($\geq 10\%$) adverse reactions in participants 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%).

In clinical studies, the most commonly reported ($\geq 10\%$) adverse reactions in participants 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

6.1 Clinical Trials Experience

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

The safety of COMIRNATY was evaluated in participants 16 years of age and older in 2 clinical studies conducted in Germany (Study 1), United States, Argentina, Brazil, Turkey, South Africa, and Germany (Study 2). Study BNT162-01 (Study 1) was a Phase 1/2, 2-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age. Study C4591001 (Study 2) is a Phase 1/2/3 multicenter, multinational, randomized, saline placebo-controlled, double-blinded (Phase 2/3), dose-finding, vaccine candidate-selection and efficacy study that has enrolled approximately 44,047 participants (22,026 COMIRNATY; 22,021 placebo) 16 years of age or older (including 378 and 376 participants 16 through 17 years of age in the vaccine and placebo groups, respectively). Upon issuance of the Emergency Use Authorization (December 11, 2020) for COMIRNATY, participants were unblinded to offer placebo participants COMIRNATY. Participants were unblinded in a phased manner over a period of months to offer placebo participants COMIRNATY. Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection; HIV-positive participants are included in safety population disposition but are summarized separately in safety analyses. Confirmed stable HIV infection was defined as documented viral load < 50 copies/mL and CD4 count > 200 cells/mm³ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

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

Participants 16 years and older in the reactogenicity subset were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received COMIRNATY and those who received placebo. Overall, among the total participants who received either COMIRNATY or placebo, 50.9% were male, 49.1% were female, 79.3% were 16 through 64 years of age, 20.7% were 65 years of age and older, 82.0% were White, 9.6% were Black or African American, 25.9% were Hispanic/Latino, 4.3% were Asian, and 1.0% were American Indian or Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days following each dose of COMIRNATY and placebo in the subset of participants 16 through 55 years of age included in the safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of COMIRNATY and placebo for participants 56 years of age and older.

In participants 16 through 55 years of age after receiving Dose 2, the mean duration of pain at the injection site was 2.5 days (range 1 to 70 days), for redness 2.2 days (range 1 to 9 days), and for swelling 2.1 days (range 1 to 8 days) for participants in the COMIRNATY group. In participants 56 years of age and older after receiving Dose 2, the mean duration of pain at the injection site was 2.4 days (range 1 to 36 days), for redness 3.0 days (range 1 to 34 days), and for swelling 2.6 days (range 1 to 34 days) for participants in the COMIRNATY group.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N [†] =2899 n [‡] (%)	Placebo Dose 1 N [†] =2908 n [‡] (%)	COMIRNATY Dose 2 N [†] =2682 n [‡] (%)	Placebo Dose 2 N [†] =2684 n [‡] (%)
Redness [§]				

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

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

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

§ Mild: > 2.0 to ≤ 5.0 cm; Moderate: > 5.0 to ≤ 10.0 cm; Severe: > 10.0 cm.

¶ Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

	COMIRNATY Dose 1 N[†]=2899 n[‡] (%)	Placebo Dose 1 N[†]=2908 n[‡] (%)	COMIRNATY Dose 2 N[†]=2682 n[‡] (%)	Placebo Dose 2 N[†]=2684 n[‡] (%)
Any (>2.0 cm)	156 (5.4)	28 (1.0)	151 (5.6)	18 (0.7)
Mild	113 (3.9)	19 (0.7)	90 (3.4)	12 (0.4)
Moderate	36 (1.2)	6 (0.2)	50 (1.9)	6 (0.2)
Severe	7 (0.2)	3 (0.1)	11 (0.4)	0
Swelling[§]				
Any (>2.0 cm)	184 (6.3)	16 (0.6)	183 (6.8)	5 (0.2)
Mild	124 (4.3)	6 (0.2)	110 (4.1)	3 (0.1)
Moderate	54 (1.9)	8 (0.3)	66 (2.5)	2 (0.1)
Severe	6 (0.2)	2 (0.1)	7 (0.3)	0
Pain at the injection site[¶]				
Any	2426 (83.7)	414 (14.2)	2101 (78.3)	312 (11.6)
Mild	1464 (50.5)	391 (13.4)	1274 (47.5)	284 (10.6)
Moderate	923 (31.8)	20 (0.7)	788 (29.4)	28 (1.0)
Severe	39 (1.3)	3 (0.1)	39 (1.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

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

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

§ Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

¶ Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 16 Through 55 Years of Age – Reactogenicity Subset of the Safety Population*

	COMIRNATY Dose 1 N[†]=2899 n[‡] (%)	Placebo Dose 1 N[†]=2908 n[‡] (%)	COMIRNATY Dose 2 N[†]=2682 n[‡] (%)	Placebo Dose 2 N[†]=2684 n[‡] (%)
Fever				
≥38.0°C	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
≥38.0°C to 38.4°C	86 (3.0)	16 (0.6)	254 (9.5)	5 (0.2)
>38.4°C to 38.9°C	25 (0.9)	5 (0.2)	146 (5.4)	4 (0.1)
>38.9°C to 40.0°C	8 (0.3)	4 (0.1)	39 (1.5)	2 (0.1)
>40.0°C	0	0	1 (0.0)	0
Fatigue[§]				
Any	1431 (49.4)	960 (33.0)	1649 (61.5)	614 (22.9)
Mild	760 (26.2)	570 (19.6)	558 (20.8)	317 (11.8)
Moderate	630 (21.7)	372 (12.8)	949 (35.4)	283 (10.5)
Severe	41 (1.4)	18 (0.6)	142 (5.3)	14 (0.5)
Headache[§]				
Any	1262 (43.5)	975 (33.5)	1448 (54.0)	652 (24.3)
Mild	785 (27.1)	633 (21.8)	699 (26.1)	404 (15.1)
Moderate	444 (15.3)	318 (10.9)	658 (24.5)	230 (8.6)
Severe	33 (1.1)	24 (0.8)	91 (3.4)	18 (0.7)
Chills[§]				
Any	479 (16.5)	199 (6.8)	1015 (37.8)	114 (4.2)
Mild	338 (11.7)	148 (5.1)	477 (17.8)	89 (3.3)
Moderate	126 (4.3)	49 (1.7)	469 (17.5)	23 (0.9)
Severe	15 (0.5)	2 (0.1)	69 (2.6)	2 (0.1)
Vomiting[¶]				
Any	34 (1.2)	36 (1.2)	58 (2.2)	30 (1.1)
Mild	29 (1.0)	30 (1.0)	42 (1.6)	20 (0.7)
Moderate	5 (0.2)	5 (0.2)	12 (0.4)	10 (0.4)
Severe	0	1 (0.0)	4 (0.1)	0
Diarrhea[#]				
Any	309 (10.7)	323 (11.1)	269 (10.0)	205 (7.6)

	COMIRNATY Dose 1 N[†]=2899 n[‡] (%)	Placebo Dose 1 N[†]=2908 n[‡] (%)	COMIRNATY Dose 2 N[†]=2682 n[‡] (%)	Placebo Dose 2 N[†]=2684 n[‡] (%)
Mild	251 (8.7)	264 (9.1)	219 (8.2)	169 (6.3)
Moderate	55 (1.9)	58 (2.0)	44 (1.6)	35 (1.3)
Severe	3 (0.1)	1 (0.0)	6 (0.2)	1 (0.0)
New or worsened muscle pain[§]				
Any	664 (22.9)	329 (11.3)	1055 (39.3)	237 (8.8)
Mild	353 (12.2)	231 (7.9)	441 (16.4)	150 (5.6)
Moderate	296 (10.2)	96 (3.3)	552 (20.6)	84 (3.1)
Severe	15 (0.5)	2 (0.1)	62 (2.3)	3 (0.1)
New or worsened joint pain[§]				
Any	342 (11.8)	168 (5.8)	638 (23.8)	147 (5.5)
Mild	200 (6.9)	112 (3.9)	291 (10.9)	82 (3.1)
Moderate	137 (4.7)	55 (1.9)	320 (11.9)	61 (2.3)
Severe	5 (0.2)	1 (0.0)	27 (1.0)	4 (0.1)
Use of antipyretic or pain medication [¶]	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

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

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

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

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

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

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

‡ Severity was not collected for use of antipyretic or pain medication.

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

	COMIRNATY Dose 1 N[†]=2008 n[‡] (%)	Placebo Dose 1 N[†]=1989 n[‡] (%)	COMIRNATY Dose 2 N[†]=1860 n[‡] (%)	Placebo Dose 2 N[†]=1833 n[‡] (%)
Redness[§]				
Any (>2.0 cm)	106 (5.3)	20 (1.0)	133 (7.2)	14 (0.8)
Mild	71 (3.5)	13 (0.7)	65 (3.5)	10 (0.5)
Moderate	30 (1.5)	5 (0.3)	58 (3.1)	3 (0.2)
Severe	5 (0.2)	2 (0.1)	10 (0.5)	1 (0.1)
Swelling[§]				
Any (>2.0 cm)	141 (7.0)	23 (1.2)	145 (7.8)	13 (0.7)
Mild	87 (4.3)	11 (0.6)	80 (4.3)	5 (0.3)
Moderate	52 (2.6)	12 (0.6)	61 (3.3)	7 (0.4)
Severe	2 (0.1)	0	4 (0.2)	1 (0.1)
Pain at the injection site[¶]				
Any (>2.0 cm)	1408 (70.1)	185 (9.3)	1230 (66.1)	143 (7.8)
Mild	1108 (55.2)	177 (8.9)	873 (46.9)	138 (7.5)
Moderate	296 (14.7)	8 (0.4)	347 (18.7)	5 (0.3)
Severe	4 (0.2)	0	10 (0.5)	0

Notes: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

No Grade 4 solicited local reactions were reported in participants 56 years of age and older.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

§ Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

¶ Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

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

	COMIRNATY Dose 1 N [†] =2008 n [‡] (%)	Placebo Dose 1 N [†] =1989 n [‡] (%)	COMIRNATY Dose 2 N [†] =1860 n [‡] (%)	Placebo Dose 2 N [†] =1833 n [‡] (%)
Fever				
≥38.0°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.1)	3 (0.2)	158 (8.5)	2 (0.1)
>38.4°C to 38.9°C	2 (0.1)	3 (0.2)	54 (2.9)	1 (0.1)
>38.9°C to 40.0°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
>40.0°C	0	0	0	0
Fatigue[§]				
Any	677 (33.7)	447 (22.5)	949 (51.0)	306 (16.7)
Mild	415 (20.7)	281 (14.1)	391 (21.0)	183 (10.0)
Moderate	259 (12.9)	163 (8.2)	497 (26.7)	121 (6.6)
Severe	3 (0.1)	3 (0.2)	60 (3.2)	2 (0.1)
Grade 4	0	0	1 (0.1)	0
Headache[§]				
Any	503 (25.0)	363 (18.3)	733 (39.4)	259 (14.1)
Mild	381 (19.0)	267 (13.4)	464 (24.9)	189 (10.3)
Moderate	120 (6.0)	93 (4.7)	256 (13.8)	65 (3.5)
Severe	2 (0.1)	3 (0.2)	13 (0.7)	5 (0.3)
Chills[§]				
Any	130 (6.5)	69 (3.5)	435 (23.4)	57 (3.1)
Mild	102 (5.1)	49 (2.5)	229 (12.3)	45 (2.5)
Moderate	28 (1.4)	19 (1.0)	185 (9.9)	12 (0.7)
Severe	0	1 (0.1)	21 (1.1)	0
Vomiting[¶]				
Any	10 (0.5)	9 (0.5)	13 (0.7)	5 (0.3)
Mild	9 (0.4)	9 (0.5)	10 (0.5)	5 (0.3)
Moderate	1 (0.0)	0	1 (0.1)	0
Severe	0	0	2 (0.1)	0
Diarrhea[#]				
Any	168 (8.4)	130 (6.5)	152 (8.2)	102 (5.6)
Mild	137 (6.8)	109 (5.5)	125 (6.7)	76 (4.1)
Moderate	27 (1.3)	20 (1.0)	25 (1.3)	22 (1.2)
Severe	4 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[§]				
Any	274 (13.6)	165 (8.3)	537 (28.9)	99 (5.4)
Mild	183 (9.1)	111 (5.6)	229 (12.3)	65 (3.5)
Moderate	90 (4.5)	51 (2.6)	288 (15.5)	33 (1.8)
Severe	1 (0.0)	3 (0.2)	20 (1.1)	1 (0.1)
New or worsened joint pain[§]				
Any	175 (8.7)	124 (6.2)	353 (19.0)	72 (3.9)
Mild	119 (5.9)	78 (3.9)	183 (9.8)	44 (2.4)

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

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

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

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

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

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

▷ Severity was not collected for use of antipyretic or pain medication.

	COMIRNATY Dose 1 N[†]=2008 n[‡] (%)	Placebo Dose 1 N[†]=1989 n[‡] (%)	COMIRNATY Dose 2 N[†]=1860 n[‡] (%)	Placebo Dose 2 N[†]=1833 n[‡] (%)
Moderate	53 (2.6)	45 (2.3)	161 (8.7)	27 (1.5)
Severe	3 (0.1)	1 (0.1)	9 (0.5)	1 (0.1)
Use of antipyretic or pain medication [‡]	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

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

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

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention. Participants with chronic, stable HIV infection were excluded.

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

‡ n = Number of participants with the specified reaction.

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

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

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

‡ Severity was not collected for use of antipyretic or pain medication.

In participants with chronic, stable HIV infection the frequencies of solicited local and systemic adverse reactions were similar to or lower than those observed for all participants 16 years of age and older.

Unsolicited Adverse Events

Overall, 11,253 (51.1%) participants in the COMIRNATY group and 11,316 (51.4%) participants in the placebo group had follow-up time between ≥4 months to <6 months after Dose 2 in the blinded placebo-controlled follow-up period with an additional 1,778 (8.1%) and 1,304 (5.9%) with ≥6 months of blinded follow-up time in the COMIRNATY and placebo groups, respectively.

A total of 12,006 (54.5%) participants originally randomized to COMIRNATY had ≥6 months total (blinded and unblinded) follow-up after Dose 2.

In an analysis of all unsolicited adverse events reported following any dose, through 1 month after Dose 2, in participants 16 years of age and older (N=43,847; 21,926 COMIRNATY group vs. 21,921 placebo group), those assessed as adverse reactions not already captured by solicited local and systemic reactions were nausea (274 vs. 87), malaise (130 vs. 22), lymphadenopathy (83 vs. 7), asthenia (76 vs. 25), decreased appetite (39 vs. 9), hyperhidrosis (31 vs. 9), lethargy (25 vs. 6), and night sweats (17 vs. 3).

In analyses of all unsolicited adverse events in Study 2 from Dose 1 up to the participant unblinding date, 58.2% of study participants had at least 4 months of follow-up after Dose 2. Among participants 16 through 55 years of age who received at least 1 dose of study vaccine, 12,995 of whom received COMIRNATY and 13,026 of whom received placebo, unsolicited adverse events were reported by 4,396 (33.8%) participants in the COMIRNATY group and 2,136 (16.4%) participants in the placebo group. In a similar analysis in participants 56 years of age and older that included 8,931 COMIRNATY recipients and 8,895 placebo recipients, unsolicited adverse events were reported by 2,551 (28.6%) participants in the COMIRNATY group and 1,432 (16.1%) participants in the placebo group. Among participants with confirmed stable HIV infection that included 100 COMIRNATY recipients and 100 placebo recipients, unsolicited adverse events were reported by 29 (29%) participants in the COMIRNATY group and 15 (15%) participants in the placebo group. The higher frequency of reported unsolicited adverse events among COMIRNATY recipients compared to placebo recipients was primarily attributed to events that are consistent with adverse reactions solicited among participants in the reactogenicity subset (Table 3 and Table 4).

Throughout the placebo-controlled safety follow-up period, Bell's palsy (facial paralysis) was reported by 4 participants in the COMIRNATY group and 2 participants in the placebo group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. In the placebo group the onset of facial paralysis was Day 32 and Day 102. Currently available information is insufficient to determine a causal relationship with the vaccine. In the analysis of blinded, placebo-controlled follow-up, there were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of non-serious adverse events that would suggest a causal relationship to COMIRNATY.

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (COMIRNATY =12,995; placebo = 13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 103 (0.8%) COMIRNATY recipients and 117 (0.9%) placebo recipients. In a similar analysis, in participants 56 years of age and older (COMIRNATY = 8,931; placebo = 8,895), serious adverse events were reported by 165 (1.8%) COMIRNATY recipients and 151 (1.7%) placebo recipients who received at least 1 dose of COMIRNATY or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after Dose 2. Among participants with confirmed stable HIV infection serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 2 (2%) COMIRNATY recipients and 2 (2%) placebo recipients.

In the analysis of blinded, placebo-controlled follow-up, 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. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of serious adverse events that would suggest a causal relationship to COMIRNATY.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of COMIRNATY, including under Emergency Use Authorization. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Gastrointestinal Disorders: diarrhea, vomiting

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COMIRNATY during pregnancy. Women who are vaccinated with COMIRNATY during pregnancy are encouraged to enroll in the registry by visiting <https://mothertobaby.org/ongoing-study/covid19-vaccines/>.

Risk Summary.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on 4 occasions; twice prior to mating and twice during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine (*see Animal Data*).

Data

Animal Data

In a developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of COMIRNATY was administered to female rats by the intramuscular route on 4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

8.2 Lactation

Risk Summary.

It is not known whether COMIRNATY is excreted in human milk. Data are not available to assess the effects of COMIRNATY on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COMIRNATY and any potential adverse effects on the breastfed child from COMIRNATY or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

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

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

8.5 Geriatric Use

Of the total number of COMIRNATY recipients in Study 2 as of March 13, 2021 (N = 22,026), 20.7% (n = 4,552) were 65 years of age and older and 4.2% (n = 925) were 75 years of age and older [*see Clinical Studies (14.1)*]. No overall differences in safety or effectiveness were observed between these recipients and younger recipients.

11 DESCRIPTION

COMIRNATY (COVID-19 Vaccine, mRNA) is a sterile suspension for injection for intramuscular use. COMIRNATY is supplied as a frozen suspension in multiple dose vials with gray caps and labels with gray borders. Each 0.3 mL dose of COMIRNATY supplied in multiple dose vials with gray caps and labels with gray borders contains 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each 0.3 mL dose of the COMIRNATY supplied in multiple dose vials with gray caps and labels with gray borders also includes the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diy)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol), 0.06 mg tromethamine, 0.4 mg tromethamine hydrochloride, and 31 mg sucrose.

COMIRNATY does not contain preservative.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The nucleoside-modified mRNA in COMIRNATY is formulated in lipid particles, which enable delivery of the mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

Efficacy in Participants 16 Years of Age and Older

Study 2 is an ongoing, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

In Study 2, based on data accrued through March 13, 2021, approximately 44,000 participants 16 years of age and older were randomized equally and received 2 doses of COMIRNATY or placebo. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

Overall, among the total participants who received COMIRNATY or placebo, 51.4% or 50.3% were male and 48.6% or 49.7% were female, 79.1% or 79.2% were 16 through 64 years of age, 20.9% or 20.8% were 65 years of age and older, 81.9% or 82.1% were White, 9.5% or 9.6% were Black or African American, 1.0% or 0.9% were American Indian or Alaska Native, 4.4% or 4.3% were Asian, 0.3% or 0.2% Native Hawaiian or other Pacific Islander, 25.6% or 25.4% were Hispanic/Latino, 73.9% or 74.1% were non-Hispanic/Latino, 0.5% or 0.5% did not report ethnicity, 46.0% or 45.7% had comorbidities [participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as subjects who had at least 1 of the Charlson comorbidity index category or body mass index (BMI) ≥ 30 kg/m²], respectively. The mean age at vaccination was 49.8 or 49.7 years and median age was 51.0 or 51.0 in participants who received COMIRNATY or placebo, respectively.

Efficacy Against COVID-19

The population for the analysis of the protocol pre-specified primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the COMIRNATY group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. The population in the protocol pre-specified primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 through 55 years of age and 56 years of age and older began enrollment from July 27, 2020, 16 through 17 years of age began enrollment from September 16, 2020, and 12 through 15 years of age began enrollment from October 15, 2020.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, vaccine efficacy against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.3, 97.6), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the COMIRNATY group compared to 162 COVID-19 cases in the placebo group.

The population for the updated vaccine efficacy analysis included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to 6 months of follow-up after Dose 2. There were 12,796 (60.8%) participants in the COMIRNATY group and 12,449 (58.7%) in the placebo group followed for ≥ 4 months after Dose 2 in the blinded placebo-controlled follow-up period.

SARS-CoV-2 variants of concern identified from COVID-19 cases in this study include B.1.1.7 (Alpha) and B.1.351 (Beta). Representation of identified variants among cases in vaccine versus placebo recipients did not suggest decreased vaccine effectiveness against these variants.

The updated vaccine efficacy information is presented in Table 5.

Table 5: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

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

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.

Subgroup	COMIRNATY N [†] =19,993 Cases n1 [‡] Surveillance Time [§] (n2 [¶])	Placebo N [†] =20,118 Cases n1 [‡] Surveillance Time [§] (n2 [¶])	Vaccine Efficacy % (95% CI [#])
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)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	COMIRNATY N [†] =21,047 Cases n1 [‡] Surveillance Time [§] (n2 [¶])	Placebo N [†] =21,210 Cases n1 [‡] Surveillance Time [§] (n2 [¶])	Vaccine Efficacy % (95% CI [#])
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.

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.

Efficacy Against Severe COVID-19

Efficacy analyses of secondary efficacy endpoints supported benefit of COMIRNATY in preventing severe COVID-19. Vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 6) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

Table 6: 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[†] or 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

Vaccine Efficacy – First Severe COVID-19 Occurrence			
	COMIRNATY Cases n1 [§] Surveillance Time [¶] (n2 [#])	Placebo Cases n1 [§] Surveillance Time [¶] (n2 [#])	Vaccine Efficacy % (95% CI ^b)
7 days after Dose 2 ^b	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition			
	COMIRNATY Cases n1 [§] Surveillance Time [¶] (n2 [#])	Placebo Cases n1 [§] Surveillance Time [¶] (n2 [#])	Vaccine Efficacy % (95% CI ^b)
7 days after Dose 2 ^b	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 high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

COMIRNATY Suspension for Intramuscular Injection, multiple dose vials with gray caps and labels with gray borders are supplied in a carton containing 10 multiple dose vials (NDC 0069-2025-10) or 25 multiple dose vials (NDC 0069-2025-25).

One vial contains 6 doses of 0.3 mL.

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

Do not refreeze thawed vials.

Vial Storage Prior to Use

Cartons of COMIRNATY multiple dose vials with gray caps and labels with gray borders will arrive frozen at ultra-cold conditions in thermal containers with dry ice.

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

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

If cartons of COMIRNATY multiple dose vials with gray caps and labels with gray borders are received at 2°C to 8°C, they should be stored at 2°C to 8°C. Check that the carton has been updated to reflect the 10-week refrigerated expiry date.

Regardless of storage condition, the vaccine should not be used after the expiration date printed on the vial and cartons.

Vial Storage During Use

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

COMIRNATY multiple dose vials with gray caps and labels with gray borders may be stored at room temperature [8°C to 25°C (46°F to 77°F)] for a total of 12 hours prior to the first puncture. After first puncture, the vial should be held between 2°C to 25°C (35°F to 77°F). Vials should be discarded 12 hours after first puncture.

DO NOT DILUTE PRIOR TO USE.

Transportation of Vials

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

17 PATIENT COUNSELING INFORMATION

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

Inform vaccine recipient of the importance of completing the 2 dose vaccination series.

There is a pregnancy exposure registry for COMIRNATY. Encourage individuals exposed to COMIRNATY around the time of conception or during pregnancy to register by visiting <https://mothertobaby.org/ongoing-study/covid19-vaccines/>.

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

This product's labeling may have been updated. For the most recent prescribing information, please visit <https://dailymed.nlm.nih.gov/dailymed/>.

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



Manufactured by
Pfizer Inc., New York, NY 10017

LAB-1490-1.0

US Govt. License No. 2229

PRINCIPAL DISPLAY PANEL - 0.3 mL Vial Label

COVID-19 Vaccine, mRNA
COMIRNATY®

Rx only

DO NOT DILUTE

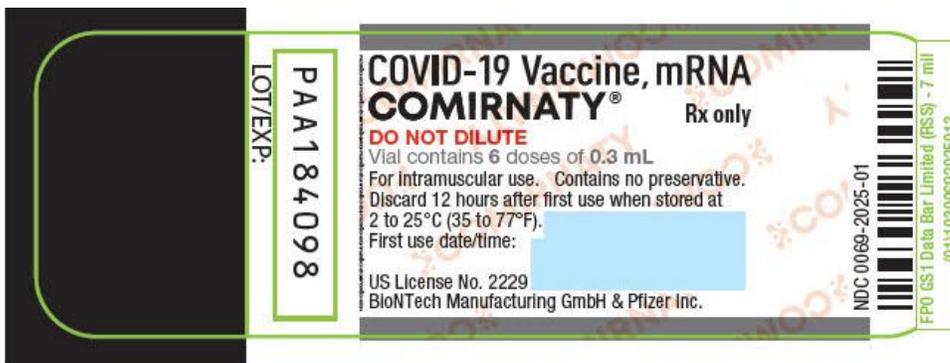
Vial contains 6 doses of 0.3 mL

For intramuscular use. Contains no preservative.
Discard 12 hours after first use when stored at
2 to 25°C (35 to 77°F).

First use date/time:

US License No. 2229

BioNTech Manufacturing GmbH & Pfizer Inc.



PRINCIPAL DISPLAY PANEL - 10 Vial Carton

NDC 0069-2025-10

COVID-19 Vaccine, mRNA
COMIRNATY®

Suspension for Injection, for Intramuscular Use

DO NOT DILUTE

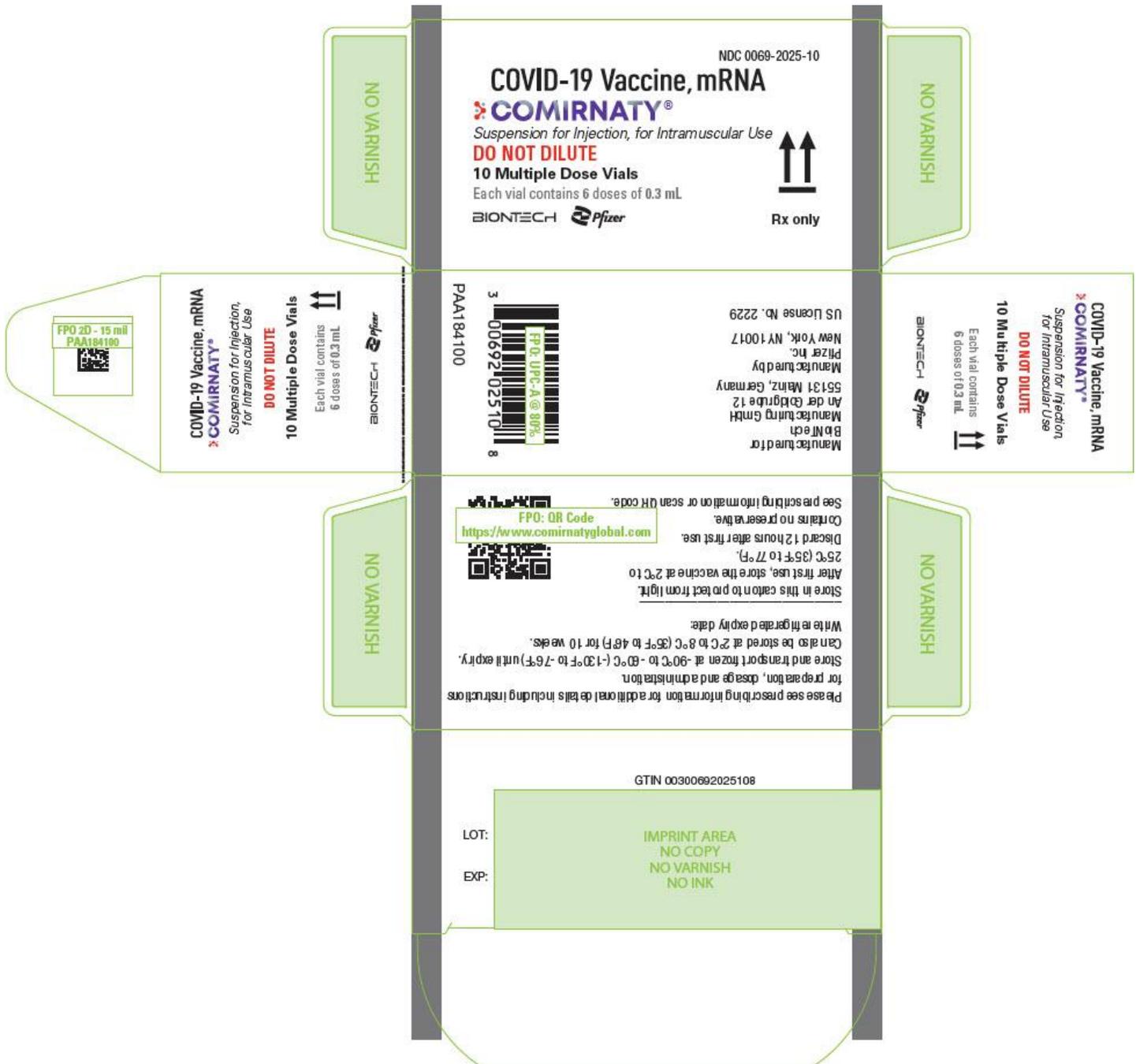
10 Multiple Dose Vials

Each vial contains 6 doses of 0.3 mL

BIONTECH

Pfizer

Rx only



PRINCIPAL DISPLAY PANEL - 25 Vial Carton

NDC 0069-2025-10

COVID-19 Vaccine, mRNA
COMIRNATY®

Suspension for Injection, for Intramuscular Use

DO NOT DILUTE

10 Multiple Dose Vials

Each vial contains 6 doses of 0.3 mL

BIONTECH

Pfizer

Rx only

NDC 0069-2025-25

COVID-19 Vaccine, mRNA
COMIRNATY®
Suspension for Injection, for Intramuscular Use
DO NOT DILUTE
25 Multiple Dose Vials
 Each vial contains 6 doses of 0.3 mL

BIONTECH **Pfizer**

Rx only

Please see prescribing information for additional details including instructions for preparation, dosage and administration.
 Store and transport frozen at -90°C to -60°C (-130°F to -76°F) until expiry.
 Can also be stored at 2°C to 8°C (35°F to 46°F) for 10 weeks.

Write refrigerated expiry date: _____
 Store in this carton to protect from light.
 After first use, store the vaccine at 2°C to 25°C (35°F to 77°F).
 Discard 12 hours after first use.
 Contains no preservative.
 See prescribing information or scan QR code.

FPD: QR Code
<https://www.comirnatyglobal.com>

LOT/EXP:

COMIRNATY®
Suspension for Injection, for Intramuscular Use
DO NOT DILUTE
25 Multiple Dose Vials
 Each vial contains 6 doses of 0.3 mL

BIONTECH **Pfizer**

Rx only

COVID-19 Vaccine, mRNA
COMIRNATY®
Suspension for Injection, for Intramuscular Use
DO NOT DILUTE
25 Multiple Dose Vials
 Each vial contains 6 doses of 0.3 mL

BIONTECH **Pfizer**

COVID-19 Vaccine, mRNA
COMIRNATY®
Suspension for Injection, for Intramuscular Use
DO NOT DILUTE
25 Multiple Dose Vials
 Each vial contains 6 doses of 0.3 mL

BIONTECH **Pfizer**

Manufactured for
 BioNTech
 Manufacturing GmbH
 Ader Goldgrube 12
 55131 Mainz, Germany
 Manufactured by
 Pfizer Inc.
 New York, NY 10017
 US License No. 2229

PAA184099

FPD: UPC-A @ 80%
 00692-02525

**COMIRNATY**

covid-19 vaccine, mrna injection, suspension

Product Information

Product Type	VACCINE	Item Code (Source)	NDC:0069-2025
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TOZINAMERAN (UNII: 5085ZFP6SJ) (TOZINAMERAN - UNII:5085ZFP6SJ)	TOZINAMERAN	0.225 mg in 2.25 mL

Inactive Ingredients

Ingredient Name	Strength
ALC-0159 (UNII: PJH39UMU6H)	0.41 mg in 2.25 mL
ALC-0315 (UNII: AVX8DX713V)	3.22 mg in 2.25 mL
SUCROSE (UNII: C151H8M554)	231.8 mg in 2.25 mL
1,2-DISTEAROYL-SN-GLYCERO-3-PHOSPHOCHOLINE (UNII: 0431PI2M0K)	0.7 mg in 2.25 mL
CHOLESTEROL (UNII: 97CST2UQ7J)	1.4 mg in 2.25 mL
WATER (UNII: 059QF0KO0R)	
TROMETHAMINE (UNII: 023C2WHX2V)	0.45 mg in 2.25 mL
TROMETHAMINE HYDROCHLORIDE (UNII: 383V75M34E)	2.97 mg in 2.25 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0069-2025-10	10 in 1 CARTON		
1	NDC:0069-2025-01	2.25 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:0069-2025-25	25 in 1 CARTON		
2	NDC:0069-2025-01	2.25 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125742	12/22/2021	

Labeler - Pfizer Laboratories Div Pfizer Inc (134489525)**Registrant** - Pfizer Inc (113480771)**Establishment**

Name	Address	ID/FEI	Business Operations
Pfizer Manufacturing Belgium NV		370156507	ANALYSIS(0069-2025) , MANUFACTURE(0069-2025) , PACK(0069-2025) , LABEL(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC		174350868	ANALYSIS(0069-2025) , API MANUFACTURE(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Inc		004954111	ANALYSIS(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
Labor LS SE & Co. KG		314929072	ANALYSIS(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
Rentschler Biopharma SE		313166479	ANALYSIS(0069-2025) , API MANUFACTURE(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Ireland Pharmaceuticals		985586408	ANALYSIS(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
BioNTech Innovative Manufacturing Services GmbH		537365801	ANALYSIS(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
BioNTech Manufacturing GmbH		314382536	ANALYSIS(0069-2025) , API MANUFACTURE(0069-2025)

Establishment

Name	Address	ID/FEI	Business Operations
BioNTech Manufacturing Marburg GmbH		313270335	ANALYSIS(0069-2025) , API MANUFACTURE(0069-2025)

Revised: 12/2021

Pfizer Laboratories Div Pfizer Inc

The Nuremberg Code (1947)

Permissible Medical Experiments

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

THE BELMONT REPORT

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human
Subjects of Research

The National Commission for the Protection of Human Subjects of
Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

**** Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

**** Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

**** Deceased.*

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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes [1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals [2]. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this

description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project [3].

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons. — Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow

prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. — Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. — Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. — Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for

needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of

such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. — The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. — Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

[1] Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2] Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3] Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

LII > U.S. Code > Title 10 > Subtitle A > PART II > CHAPTER 55 > § 1107

10 U.S. Code § 1107 - Notice of use of an investigational new drug or a drug unapproved for its applied use

U.S. Code Notes State Regulations

(a) NOTICE REQUIRED.—

(1) Whenever the Secretary of Defense requests or requires a member of the armed forces to receive an investigational new drug or a drug unapproved for its applied use, the Secretary shall provide the member with notice containing the information specified in subsection (d).

(2) The Secretary shall also ensure that health care providers who administer an investigational new drug or a drug unapproved for its applied use, or who are likely to treat members who receive such a drug, receive the information required to be provided under paragraphs (3) and (4) of subsection (d).

(b) TIME OF NOTICE.—

The notice required to be provided to a member under subsection (a)(1) shall be provided before the investigational new drug or drug unapproved for its applied use is first administered to the member.

(c) FORM OF NOTICE.—

The notice required under subsection (a)(1) shall be provided in writing.

(d) CONTENT OF NOTICE.—The notice required under subsection (a)(1) shall include the following:

(1) Clear notice that the drug being administered is an investigational new drug or a drug unapproved for its applied use.

(2) The reasons why the investigational new drug or drug unapproved for its applied use is being administered.

(3) Information regarding the possible side effects of the investigational new drug or drug unapproved for its applied use, including any known side effects possible as a result of the interaction of such drug with other drugs or treatments being administered to the members receiving such drug.

(4) Such other information that, as a condition of authorizing the use of the investigational new drug or drug unapproved for its applied use, the Secretary of Health and Human Services may require to be disclosed.

(e) RECORDS OF USE.—The Secretary of Defense shall ensure that the medical records of members accurately document—

(1) the receipt by members of any investigational new drug or drug unapproved for its applied use; and

(2) the notice required by subsection (a)(1).

(f) LIMITATION AND WAIVER.—

(1) In the case of the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation, the requirement that the member provide prior consent to receive the drug in accordance with the prior consent requirement imposed under section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)) may be waived only by the President. The President may grant such a waiver only if the President determines, in writing, that obtaining consent is not in the interests of national security.

(2) The waiver authority provided in paragraph (1) shall not be construed to apply to any case other than a case in which prior

consent for administration of a particular drug is required by reason of a determination by the Secretary of Health and Human Services that such drug is subject to the investigational new drug requirements of section 505(i) of the Federal Food, Drug, and Cosmetic Act.

(3) The Secretary of Defense may request the President to waive the prior consent requirement with respect to the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation. With respect to any such administration—

(A) the Secretary may not delegate to any other official the authority to request the President to waive the prior consent requirement for the Department of Defense; and

(B) if the President grants the requested waiver, the Secretary shall submit to the chairman and ranking minority member of each congressional defense committee a notification of the waiver, together with the written determination of the President under paragraph (1) and the Secretary's justification for the request or requirement under subsection (a) for the member to receive the drug covered by the waiver.

(4) In this subsection:

(A) The term "relevant FDA regulations" means the regulations promulgated under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)).

(B) The term "prior consent requirement" means the requirement included in the relevant FDA regulations pursuant to section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)).

(g) DEFINITIONS.—In this section:

(1) The term "investigational new drug" means a drug covered by section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)).

(2) The term “drug unapproved for its applied use” means a drug administered for a use not described in the approved labeling of the drug under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

(Added Pub. L. 105–85, div. A, title VII, § 766(a), Nov. 18, 1997, 111 Stat. 1827; amended Pub. L. 105–261, div. A, title VII, § 731(a)(1), (b), Oct. 17, 1998, 112 Stat. 2070, 2071; Pub. L. 106–65, div. A, title X, § 1067(1), Oct. 5, 1999, 113 Stat. 774; Pub. L. 108–136, div. A, title X, § 1043(b)(7), Nov. 24, 2003, 117 Stat. 1611; Pub. L. 108–375, div. A, title VII, § 726(a), Oct. 28, 2004, 118 Stat. 1992.)

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