

**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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Subject: Review of Revised Pharmacovigilance Plan

Sponsor: Pfizer

Product: COMIRNATY (Pfizer-BioNTech COVID-19 Vaccine)

BLA Number: 125742.45

Proposed Indication: Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥ 12 years of age.

Submission Date: December 16, 2021

Action Due Date: June 17, 2022

1 Objective and Scope

The purpose of this review is to assess the adequacy of the sponsor's revised pharmacovigilance plan (PVP) submitted under BLA supplement 125742/45, which proposes to extend use of Comirnaty to individuals 12 years of age and older (from the current 16 years and older licensed indication). This review provides recommendations for post-approval safety monitoring for use of Comirnaty in individuals 12 years of age and older, should it be approved, and identifies potential safety issues associated with the use of the vaccine in individuals 12 years of age and older that may need to be addressed through additional pharmacovigilance activities including postmarketing safety-related studies.

2 Product Information

2.1 Product Description

Comirnaty* contains a nucleoside-modified messenger RNA (modRNA; 30 mcg per dose) that encodes the viral spike (S) glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is a PBS Sucrose formulation (purple cap) that must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each 0.3 ml dose includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

There is also a Tris Sucrose formulation (gray cap; not diluted prior to use) in which the formulation buffer has been changed from phosphate buffered saline to Tris buffer without sodium chloride and potassium chloride while maintaining the same target pH. Excipients for the 30-mcg dose are ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, and sucrose. In addition, there is a Tris Sucrose product formulation that contains 10 mcg modRNA per dose for individuals 5 to 11 years of age. The Tris Sucrose formulation (10 mcg modRNA) for individuals 5 to 11 years of age is not interchangeable with Comirnaty or Pfizer-BioNTech COVID-19 Vaccine for ages 12 years and older.

*Note: For purposes of this memo, Comirnaty is used interchangeably with Pfizer-BioNTech COVID-19 Vaccine and BNT162b2 (product used in clinical development program).

2.2 Indication and Dosing Regimen

Comirnaty is approved for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals ≥ 16 years of age. The vaccine is

administered intramuscularly as a primary series of two doses (0.3 ml) given three weeks apart.

The product is currently authorized for use under an EUA for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 years of age and older. In addition, a third dose of the product is authorized for use under an EUA for individuals 5 years of age and older who have undergone solid organ transplant or who are diagnosed with conditions considered to have an equivalent level of immunocompromise. The EUA has also been amended to include booster doses for select populations.

Reviewer comment: Please see Section 4 of this memo and the EUA letter of authorization for additional details regarding EUA indications.

2.3 Proposed Indication

The proposed BLA supplement indication for Comirnaty is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals 12 years of age and older.

Reviewer comment: Please see the final label submitted by the sponsor for the final agreed upon language for the indication and dosing regimen.

3 Materials Reviewed

- Pharmacovigilance Plan, Version 1.4 (BLA 125742/45, Module 1.16, dated December 15, 2021; received December 16, 2021)
- Pharmacovigilance Plan, Version 1.4.1, combined PVP for PBS Sucrose and Tris Sucrose product formulations (BLA 125742/45/9, Module 1.16, dated April 29, 2022; received May 2, 2022)
- Cumulative Analysis of Post-Authorization Adverse Event Reports in Individuals Aged Between 12 and 15 Year of Age (BLA 125742/45, Module 5.3.6, dated December 1, 2021; received December 16, 2021)
- Clinical Overview (BLA 125742/45, Module 2.5; received December 16, 2021)
- Draft Label (BLA 125742/45, Module 1.14; received December 16, 2021)
- Approval Letter for Comirnaty BLA 125742/0 (dated August 23, 2021)
- Sponsor's IR responses
 - IR response regarding narratives and preferred terms (PTs) for death reports (BLA 125742.45.3; received March 1, 2022)
 - IR response regarding age eligibility for Pregnancy Registry Study (PMC #10) (BLA 125742/45/10; received May 4, 2022)
- VAERS database and data mining

4 Summary of Pertinent Regulatory History and Prior Marketed Experience

Pertinent regulatory history is shown in Table 1. Per the sponsor’s PVP, approximately 1,709,812,866 doses of BNT162b2 were shipped worldwide from receipt of the first temporary authorization for emergency supply on December 1, 2020 through September 30, 2021, including 270,020,505 doses shipped to the U.S. Per the sponsor’s Clinical Overview, as of December 2021, BNT162b2 (30 mcg) has received temporary authorization for emergency use, conditional marketing authorization approval, or full approval in >90 countries globally. As of March 8, 2022, more than 327 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. ([CDC COVID Data Tracker](#), accessed on March 9, 2022). Among all COVID-19 vaccines, 17,170,136 individuals aged 12-17 years have received at least one dose and 14,641,529 are fully vaccinated in the U.S. ([CDC COVID Data Tracker](#), accessed on March 9, 2022).

Table 1: Pertinent Regulatory History

Date	Regulatory Action
April 29, 2020	IND for BNT162b2 became effective
July 7, 2020	Fast Track Designation granted for individuals 18 years of age and older
December 11, 2020	EUA 27034 granted for active immunization to prevent COVID-19 in individuals 16 years of age and older
May 10, 2021	FDA re-issued EUA letter to expand authorization for use in individuals 12 through 15 years of age with addition of following warning in Fact Sheet for Healthcare Providers: “Syncope (fainting) may occur in association with administration of injectable vaccines, in particular adolescents. Procedures should be in place to avoid injury from fainting.”
June 25, 2021	EUA Fact Sheet revised to add Warnings for myocarditis and pericarditis following use of Pfizer-BioNTech COVID-19 Vaccine
August 12, 2021	EUA granted for third dose of BNT162b2 for individuals 12 years of age and older who have undergone solid organ transplant or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise
August 23, 2021	Approval of original BLA 125742/0 for use of Comirnaty in individuals aged 16 years and older which included safety related postmarketing requirements (PMRs # 4 - 9) for evaluation of the serious risks of myocarditis and pericarditis, and subclinical myocarditis, as well as postmarketing commitments (PMCs), including a pregnancy registry study (C4591022, PMC #10) and an

	active safety surveillance study in the Veteran's Affairs Health System (PMC #12)
September 22, 2021	EUA granted for booster dose of Comirnaty or Pfizer-BioNTech COVID-19 Vaccine at least six months after completing the primary series of this vaccine in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2
October 20, 2021	EUA Letter of Authorization (LOA) clarified eligibility for a booster dose of Comirnaty or Pfizer-BioNTech COVID-19 Vaccine and authorized administration of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 Vaccine
October 29, 2021	EUA expanded for use of product in children 5-11 years of age and authorized manufacturing change to include additional formulation using a Tris Sucrose buffer instead of PBS
November 19, 2021	EUA expanded use of product as a single booster dose in individuals 18 years and older at least 6-months after completing the primary series of this vaccine (homologous booster) and as a heterologous booster
December 9, 2021	EUA expanded use of product as a single booster dose in individuals aged 16 and 17 years at least 6-months after completing the primary series of this vaccine
December 16, 2021	BLA supplement approved to include a new 30-mcg dose formulation of Comirnaty that uses a Tris Sucrose buffer instead of a PBS buffer
January 3, 2022	EUA LOA re-issued to authorize use of vaccine as a single booster dose in individuals aged 12-15 years, lowered dosing interval for the homologous booster to at least 5-months after completion of the primary series, and authorized a third primary series dose of the vaccine at least 28-days following the 2-dose regimen for individuals aged 5-11 years who have undergone solid organ transplantation or who have an equivalent level of immunocompromise
March 29, 2022	EUA re-issued to authorize second booster dose to individuals aged 50 years and older or individuals ≥ 12 years of age with certain kinds of immunocompromise at least 4 months after receipt of the first booster dose of any FDA authorized or approved COVID-19 vaccine

5 Summary of Sponsor's Safety Database

5.1 Clinical Studies

The sponsor evaluated the safety and immunogenicity of BNT162b2 among individuals 12-15 years of age in Phase 1/2/3 Study C4591001 (pivotal study for individuals ≥ 12 years of age). Phase 1 was the dose finding portion of the study that evaluated dose levels for two vaccine candidates (BNT162b1 and BNT162b2) in the U.S. BNT162b2 (30 mcg dose) was selected to advance to a Phase 2/3 study which evaluated efficacy and safety of a 30 mcg two-dose series of BNT162b2 three-weeks apart and included 2264 randomized participants 12-15 years of age (1:1 randomization: 1134 vaccine recipients and 1130 saline placebo recipients; all adolescents were enrolled in the U.S.). Participants 12-15 years of age were unblinded when they became locally eligible for vaccination and wished to know their randomization status; placebo participants were offered BNT162b2 and unblinded follow-up continued for all study participants. The safety evaluation included assessment of reactogenicity and antipyretic use for 7-days after each dose via e-diary. Adverse events (AEs) were collected for up to 1-month post-dose 2 and serious AEs (SAEs) were collected for up to 6-months post-dose 2 (deaths were recorded to the end of the study). Myocarditis and pericarditis were AEs of special interest (AESIs). Cumulative safety data were reported from Dose 1 to at least 6-months after Dose 2 through the data cut-off (September 2, 2021). Follow-up will continue for at least two years and/or end of study, except for those who enrolled in Study C4591031 for booster dose evaluation.

Reviewer comment: Please see the clinical review memo for additional details regarding the FDA clinical safety evaluation of BNT162b2 in individuals 12-15 years of age.

5.2 Adverse Events from the Clinical Safety Database

The safety population included 2260 participants 12-15 years of age (1131 BNT162b2 recipients and 1129 placebo recipients; four study participants did not receive any study intervention and were excluded). For Phase 2/3, the median follow-up during the blinded placebo-controlled period was 4.4 months. From Dose 2 to the data cut-off date, most (n=740, 65.4%) of BNT162b2 group participants had a total follow-up time of ≥ 8 to < 10 months (blinded and unblinded). Most reactogenicity AEs were mild or moderate in severity and were self-limited. AEs from Dose 1 to unblinding were similar between BNT162b2 and placebo recipients (8.45% vs. 10.0%, respectively). The most frequently reported AEs in BNT162b2 recipients were lymphadenopathy (n=9, 0.8%), injection site pain (8, 0.7%), fatigue (8, 0.7%), pyrexia (6, 0.5%), depression (6, 0.5%), nausea (5, 0.4%), and headache (5, 0.4%). Psychiatric disorder AEs were similar between BNT162b2 and placebo recipients (1.5% vs 1.2%, respectively); depression was reported for 6 (0.5%) BNT162b2 recipients and 3 (0.3%) placebo recipients. Four study participants were hospitalized with suicidal ideation; all four were BNT162b2 recipients and had an ongoing past medical history of depression and/or anxiety. One BNT162b2 participant had an AE leading to study withdrawal (pyrexia of 40.4° C on Day 2 post-Dose 1; resolved on Day 4).

From Dose 1 to the unblinding date, SAEs were reported for 10 (0.9%) BNT162b2 recipients (n=1131) and 2 (0.2%) placebo recipients (n=1129); there were no deaths reported. None of the SAEs were considered related to the product by study investigators. PTs reported for the SAEs among the 10 BNT162b2 recipients included suicidal ideation (n=4, 0.4%), depression (3, 0.3%), and one (0.1%) each of conversion disorder, anxiety, abdominal pain, constipation, anal abscess, and femur fracture. PTs reported for the SAEs among the 2 placebo recipients included appendicitis (n=2, 0.2%) and focal peritonitis (n=1, 0.1%). Multiple PTs could be reported for any individual subject.

Among participants who originally received placebo and then received BNT162b2 after unblinding (n=1010) there were 6 (0.6%) participants who experienced SAEs from Dose 3 (first dose of BNT162b2) to the data cut-off. One participant experienced an SAE considered related to the product by study investigators (appendicitis on Day 4 after Dose 4 [Dose 2 of BNT162b2]). In addition, there was one SAE of myocarditis which occurred in a 16-year-old male who experienced chest pain on Day 3 after Dose 4 (2nd dose BNT162b2). This individual had a one-week history of fever, cough, rhinorrhea; a respiratory virus panel was PCR positive for rhinovirus (SARS-CoV-2 RNA PCR was negative). His chest pain resolved within 24-hours of receiving ketorolac and he was discharged home after 2-days of hospitalization; cardiology follow-up indicated that the condition had resolved. The study investigator did not consider the event related to the study intervention, although the sponsor commented that they consider it a reasonable possibility that the myocarditis event was related to BNT162b2 considering the prior reports of myocarditis/pericarditis among recipients of mRNA vaccines. Other SAEs among participants who originally received placebo and then received BNT162b2 after unblinding included one event each of traumatic renal injury, epilepsy, somnolence, and major depression; none of these SAEs were considered related to BNT162b2 by study investigators. No deaths were reported.

Among other AEs of interest, lymphadenopathy was reported in nine BNT162b2 participants and two placebo participants during the blinded placebo-controlled follow-up period; events were mild or moderate in severity and most occurred in the arm and neck region. No cases of anaphylaxis, hypersensitivity, or Bell's palsy were reported during the blinded placebo-controlled period. As of the data cut-off, there were no thromboembolic or intravascular coagulation events, autoimmune or demyelination events, meningitis, encephalitis, optic neuritis, Kawasaki's disease, severe COVID-19 infection, multisystem inflammatory syndrome in children (MIS-C), or acute respiratory distress syndrome events.

Reviewer comment: Lymphadenopathy and myocarditis/pericarditis are labeled events. Review of the sponsor's clinical trial safety data among children 12-15 years of age did not reveal new safety concerns that need to be addressed in the PVP.

5.3 Review of Sponsor's Cumulative Analysis of Post-Authorization Adverse Event Reports for Individuals Aged 12-15 Years

The sponsor submitted a cumulative analysis of post-authorization AE reports from the Pfizer global safety database for BNT162b2 among individuals aged 12-15 years (received through September 30, 2021). Among 629,525 total reports, there were a total of 3,320 (1,606 U.S.) reports concerning individuals 12-15 years of age, including 1,215 (36.6%) serious reports (259 U.S.) of which 18 (0.5%) were death reports (5 U.S.). Among all reports, there was a total of 10,050 AEs reported among individuals 12-15 years of age; the most frequently reported PTs (>5%) were pyrexia (17.4%), headache (15.7%), fatigue (10.4%), poor quality product administered (8.3%), nausea (8.1%), pain in extremity (6.8%), vomiting (5.9%), malaise (5.7%), dizziness (5.5%), and chest pain (5.4%).

The 5 U.S. death reports are summarized as follows:

- A columnist reported that a 13-year-old male experienced sudden death post-dose 2
- 13-year-old male died 3-days post-dose 2; report indicated that the autopsy result showed (b) (6)
- 13-year-old male died in his sleep 3-days post-dose 2; autopsy being performed, and it was reported that information was being sent to CDC
- Reporter read a media headline that a 13-year-old (might have been a boy) died in his sleep following an unknown dose of the Pfizer vaccine and that CDC was investigating
- 13-year-old female died of unknown cause post-dose 2

Reviewer comment: The five U.S. death reports received by the sponsor contained limited clinical details. Four of the five reports seem to refer to the same unique 13-year-old male, (b) (6)

(b) (6)

Review of the 13 foreign death reports, revealed that 10 reports contained limited clinical details with unknown/unclear causes of death. Two reports indicated septic shock in patients with multiple co-morbidities, including one report of an individual who experienced status epilepticus, multiorgan failure, pulmonary hemorrhage, and disseminated intravascular coagulation (DIC). One additional report concerned a 15-year-old female with a history of asthma, Barlow's syndrome (i.e., mitral valve prolapse), and Marfan's syndrome who experienced cardiac arrest and cerebral anoxia; cardiac MRI favored Takotsubo, and the report indicated that myocarditis was unlikely with infective and immunological work-up negative. This individual also had a positive

COVID-19 serology (anti-S, anti-N, and IgM), and the report mentioned a COVID-19 infection starting at the same time as vaccination; autopsy was not performed.

Among risks identified in the PVP, the sponsor's search of the safety database through September 30, 2021 found 43 (1.3%; 8 U.S. reports) reports of anaphylactic reaction/shock (PVP: important identified risk) or anaphylactoid reaction/shock among individuals 12-15 years of age; all were serious events and there were no fatal events. No events were considered to be Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) (PVP: important potential risk) among individuals 12-15 years.

There were 180 reports of myocarditis and pericarditis (PVP: important identified risk) among individuals aged 12-15 years, including 154 (4.6%) reports of myocarditis and 61 (1.2%) reports of pericarditis (35 reports involved patients with both myocarditis and pericarditis). Among the 154 reports of myocarditis (26 U.S. reports), almost all (n=153, 99.4%) were serious; none reported a fatal outcome. The majority of reports were for males (n=131); the median age of patients was 14 years (range=12-15 years). Most cases occurred after the 2nd dose (n=106, 68.8%); 36 (23.4%) cases occurred after the 1st dose and 12 (7.8%) cases occurred after an unknown dose. Time to onset was reported for 108 cases; most events (n=101, 93.5%) occurred within 14-days post-vaccination. Most events had an outcome of resolved/resolving (n=79, 51.3%); 17 (11.0%) events were not resolved at the time of the report, and 58 (37.7%) events had an unknown outcome. Fourteen reports were classified by the sponsor as Brighton Collaboration (BC; version 1.5.0, July 16, 2021) level 1 (definitive case), nine were BC level 2 (probable case), 130 were BC level 4 (reported event but insufficient evidence to meet case definition), and one was BC level 5 (not a case).

Among the 61 (1.2%) reports of pericarditis (4 U.S. reports), all were serious (no deaths). The majority of reports were for males (n=48, 78.7%); the median age of patients was 14 years (range=12-15 years). Most cases occurred after the 2nd dose (n=38, 62.3%); 14 (23.0%) cases occurred after the 1st dose and 9 (14.8%) cases occurred after an unknown dose. Time to onset was reported for 32 cases; most events (n=28, 87.5%) occurred within 14-days post-vaccination. The outcome was unknown for most events (n=33, 54.1%); 18 (29.5%) events had an outcome of resolved/resolving, 1 (1.6%) event was resolved with sequelae, and 9 (14.8%) events were not resolved at the time of reporting. One report was classified by the sponsor as BC level 1 (BC version 1.0.0, July 15, 2021), four were BC level 2, and 56 were BC level 4.

Among areas of the PVP considered as "Missing Information" (use of product in pregnancy/lactation, vaccine effectiveness, and use in pediatric individuals <5 years of age) there was one report concerning use of the product in pregnancy/lactation among individuals aged 12-15 years. This foreign report concerned a 12-year-old patient who experienced a miscarriage two weeks post-1st dose. Regarding lack of vaccine effectiveness, there were 29 reports (14 U.S. reports) among individuals 12-15 years of age, including 20 reports (19 serious) with the PT drug ineffective and 9 reports (all serious) with the PT vaccination failure; none were death reports.

Among individuals <5 years of age (PVP: missing information), there were 56 reports (13 U.S. reports) including 14 (25.0%) serious reports; two (3.6%) reports included fatal outcomes. The two fatal reports were both foreign reports with limited information: one report of a 5-month-old male who died 15-days after his first dose and one report of a 2-year-old female who had been hospitalized since February 14, 2021, received her 2nd dose on February 25, 2021, and subsequently died on March 3, 2021. The most frequently reported PTs in the <5-year age group were product administered to patient of inappropriate age (n=21), off label use (n=17), product use issue (n=15), pyrexia (n=11), and fatigue, headache, myalgia, and nausea (n=4 each).

Reviewer comment: Review of data from the sponsor's safety database for individuals 12-15 years of age did not reveal new safety concerns that need to be addressed in the PVP.

6 Summary of FDA Post-Authorization Safety Data

6.1 Vaccine Adverse Event Reporting System (VAERS) Data

The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following the Pfizer-BioNTech COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of March 9, 2022, VAERS received 676,758 reports (including 363,690 U.S. reports) for the Pfizer-BioNTech COVID-19 Vaccine, of which 8,971 U.S. reports were in children 5-11 years of age, 14,229 U.S. reports were in children 12-15 years of age, and 7,742 U.S. reports were in children 16-17 years of age. Among the 14,229 U.S. reports for children 12-15 years of age, 1,357 were non-fatal serious and 23 were death reports.

Reviewer comment: The 23 death reports concerned 18 unique individuals. All death reports were individually reviewed. There were four unique death reports that included PTs for myocarditis/pericarditis; these reports are summarized in the myocarditis and pericarditis section below. The other 14 unique death reports were reviewed to form a clinical impression of the event described in the report. For some reports there were limited clinical details provided with no additional medical records or autopsy reports available at the time of review. Clinical impressions of the events are summarized as follows: ruptured cerebral aneurysm (2), suicide (1), COVID-19 pneumonia (1), bilateral pulmonary emboli (described as "air bubbles not DVT") (1), epithelioid sarcoma (1),

acute intracerebral hemorrhage due to chronic small vessel vasculopathy of brain in individual with Trisomy 18 (1), sudden death in individual with epilepsy and congenital microcephaly (1), unknown (1), static encephalopathy with intractable seizures and possible sepsis in individual with neuromuscular disorder and tracheostomy (1), hypertrophic cardiomyopathy in individual with recent COVID-19 infection (1), brainstem herniation from intracranial hemorrhage in individual positive for COVID-19 (1), stress cardiomyopathy (1), and heart failure (1).

The above individual with (b) (6) was a 15-year-old male with (b) (6) (b) (6) acne who experienced (b) (6) and then was (b) (6) (b) (6) within 48 hours of his 2nd dose of the Pfizer-BioNTech COVID-19 vaccine (VAERS #1382906). (b) (6)

(b) (6) The autopsy report indicated (b) (6) and (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) The autopsy report (b) (6) (b) (6) (b) (6)

VAERS queries were run using the PT Report, which showed the top ten most frequently reported MedDRA PTs to be as follows (Note: A report may have one or more PTs; queries run on March 9, 2022):

- Most frequent PTs among all ages: SARS-CoV-2 test, headache, fatigue, pyrexia, dizziness, pain, COVID-19, nausea, chills, and pain in extremity
- Most frequent PTs among individuals ≤17 years of age: dizziness, headache, pyrexia, syncope, nausea, product administered to patient of inappropriate age, chest pain, fatigue, vomiting, and product storage error
- Most frequent PTs among individuals 12-15 years of age: dizziness, pyrexia, headache, syncope, nausea, chest pain, product storage error, fatigue, vomiting, and product administered to patient of inappropriate age.

Reviewer comment: The most frequently reported PTs, including among individuals 12-15 years of age, concern labeled events, PTs related to labeled events, product storage or use issues, non-specific symptoms, or COVID-19 diagnosis/testing. The label contains instructions for storage/handling, product preparation, and administration. Review of the most frequently reported PTs did not identify new safety concerns.

In addition, safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that are labeled events.

Anaphylaxis:

Post-authorization surveillance identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.^{1,2} Anaphylaxis is an important identified risk in the PVP and is included in the label (Section 4 Contraindications, Section 5 Warnings and Precautions, 5.1 Management of Acute Allergic Reactions, Section 6.2 Postmarketing Experience). An automated VAERS query run on March 9, 2022 (which includes cases for which diagnosis and outcomes were not confirmed) for the PTs anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock returned a total of 7,582 reports, including 6,721 non-fatal serious reports and 58 death reports. Among U.S. reports, there have been a total of 1,589 reports, including 773 non-fatal serious reports and 16 death reports. Among U.S. children aged 12-15 years, there were 43 total reports of anaphylactic/anaphylactoid reaction, including 14 non-fatal serious reports (no deaths). The estimated crude reporting rate for anaphylaxis after receipt of Pfizer-BioNTech COVID-19 vaccination among all ages in the U.S. is 4.9 cases per million doses administered based on the above VAERS data and 327,525,429 doses of Pfizer-BioNTech COVID-19 Vaccine administered among all ages in the U.S. ([CDC COVID Data Tracker](#), accessed on March 9, 2022). The estimated rate of anaphylaxis following Pfizer-BioNTech COVID-19 vaccination is similar to estimated rates for other vaccines, including any influenza vaccine (1.53 cases per million doses), any tetanus diphtheria acellular pertussis vaccine (2.07 cases per million doses), and measles mumps rubella vaccine (5.14 cases per million doses).³

Myocarditis and pericarditis:

Post-EUA safety surveillance reports received by FDA and CDC identified increased rates of myocarditis and pericarditis, particularly within 7 days following administration of the second dose of the 2-dose primary series. Reporting rates for medical chart-confirmed (i.e., verified to meet CDC case definition) myocarditis and 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 through 17 years of age (~70.2 verified cases per million doses within 7-days following dose 2 administration among males ages 16-17 years and 45.7 verified cases per million doses within 7-days following dose 2 among males ages 12-15 years as per CDC presentation to the ACIP on January 5, 2022).

Although some cases of vaccine-associated myocarditis/pericarditis have 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, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

Reviewer comment: CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. Surveys are conducted at least 90 days after the onset of myocarditis symptoms. Preliminary data from this surveillance showed that among individuals aged 12-29 years who completed the survey (approximately 360 individuals), most reported no impact on their quality of life (measures included ability to perform self-care and usual activities, mobility, pain, and anxiousness or depression) and did not report missing school or work (presented at ACIP meeting on February 4, 2022). Thirteen (4%) patients reported readmission to the hospital, including 8 of 13 (62%) patients who were readmitted because of a concern with the heart. Seventy-one (20%) patients were prescribed medication for their heart as of their last appointment with the provider. Among the healthcare providers who completed the survey (n=380), most (81%) indicated the patient was probably fully or fully recovered. There were no known vaccine-associated myocarditis deaths. CDC has ongoing efforts to continue patient follow-up and contact patients with myocarditis who were not yet recovered at the time of the survey.

Myocarditis and pericarditis were added as important identified risks in the PVP and included in the label (Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis, Section 6.2 Postmarketing Experience). The Sponsor is conducting additional post-authorization/postmarketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis. As of March 9, 2022, based on automated search of VAERS (which includes cases for which diagnosis and outcomes were not confirmed), there have been a total of 15,932 reports of myocarditis and pericarditis (3,071 U.S.) following vaccination with the Pfizer-BioNTech COVID-19 Vaccine reported to VAERS, including 14,967 non-fatal serious reports (2,281 U.S.) and 206 death reports (53 U.S.). PTs included in the automated VAERS query were as follows: autoimmune myocarditis, autoimmune pericarditis, eosinophilic myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, and pleuropericarditis.

Among individuals 12-15 years of age, summary statistics for U.S. VAERS reports of myocarditis/pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine are as follows:

- 528 total U.S. reports, including 445 (84.2%) serious and 5 (0.9%) death reports
 - 465 (88.1%) male and 63 (11.9%) female
 - Median age=14 years (range=12-15 years)
 - Median onset post-vaccination=2 days* (range=0-238 days)
 - 478 (90.5%) events occurred within a 0-7 day* risk window post-vaccination
 - By dose number: Dose 1=83 (15.7%) reports; Dose 2=354 (67.0%) reports; Dose 3=25 (4.7%) reports; Unknown/Missing Dose= 66 (12.5%) reports
- *Based on calculated VAERS dates.

U.S. VAERS reports of myocarditis/pericarditis following the Pfizer-BioNTech COVID-19 Vaccine with an outcome of death among individuals 12-15 years of age (n=5 reports for 4 unique individuals) are summarized below:

- 1406840 (U.S.): 13-year-old male with past medical history (PMH) of (b) (6) (b) (6) and then was found deceased 3-days post-dose 2. Autopsy report findings (b) (6)

Reviewer Comment: (b) (6)
 (b) (6) Based on the information available in VAERS, it appears likely this individual died from (b) (6)

- 1505250 (U.S.): 13-year-old female with history of asthma, (b) (6) (b) (6) experienced (b) (6) (b) (6) (b) (6) EMS arrived and cardioverted the individual who became responsive and started answering

questions; she subsequently experienced ventricular tachycardia, pulseless ventricular tachycardia, and pulseless electrical activity and died (b) (6)

(b) (6) She had taken one dose of Dramamine the evening prior to the event.

The autopsy reported cause of death was (b) (6)

(b) (6) COVID-19 PCR testing was negative.

(b) (6)

Reviewer Comment: (b) (6)

(b) (6)

- 1764974 (U.S.): 15-year-old male with PMH of (b) (6) experienced brief unilateral shoulder pain 5-days post-dose 2; no chest pain, shortness of breath, or palpitations. The individual was swinging from a rope swing at a pond, flipping in the air, and landing in the water feet first. Individual surfaced, laughed, told his friends "Wow, that hurt!", then swam toward shore, underwater as was his usual routine; he did not re-emerge, and his body was retrieved by local authorities more than an hour later. He died 6-days post-dose 2. Autopsy report pertinent findings included the following: (b) (6)

(b) (6)

(b) (6)

(b) (6)

This case was also sent for evaluation with (b) (6)
(b) (6) Hospital. Their report indicated (b) (6)
(b) (6)

*Reviewer Comment: This individual died from (b) (6)
(b) (6) This case had three independent
autopsy evaluations. Autopsy findings noted (b) (6)
(b) (6)*

(b) (6) *One autopsy evaluation indicated (b) (6)*
(b) (6)

(b) (6)

- 1446789 (U.S.): 15-year-old male with PMH of autism, ADHD, (b) (6)
(b) (6) experienced coughing that began just prior to dose 2; he was seen by his primary care provider 6-days post-dose 2 and chest x-ray showed fluid in the lungs and possible pneumonia. He did not improve on albuterol and antibiotics and subsequently developed decreased appetite, decreased urine output, a couple of episodes of post-tussive emesis with blood-tinged secretions, abdominal pain, increased coughing, and shortness of breath. He did not have a fever or rash. He fell and hit his head on a wall, couldn't breathe, and was taken to the ED. He experienced cardiac arrest x2 at the hospital and was resuscitated, intubated and air transported to another hospital for further care. (b) (6)
(b) (6)

(b) (6)

(b) (6) and he died approximately 2.5 months after hospitalization.

Reviewer Comment: This individual with a history of autism, ADHD, (b) (6) (b) (6) experienced acute decompensated heart failure with a complicated hospital course. His symptoms began just prior to Pfizer-BioNTech COVID-19 vaccine dose 2; (b) (6) noted that (b) (6)

(b) (6) He was evaluated for an

(b) (6)

(b) (6) findings on autopsy included (b) (6)

(b) (6)

(b) (6)

Review of the above VAERS data, as well as ongoing review of VAERS data and the sponsor's periodic safety reports, did not identify new safety concerns among individuals aged 12-15 years. Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and consistent with the known safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

6.2 Data Mining Findings

Data mining of the VAERS database using Empirica Signal¹ with a data lock point of March 4, 2022, revealed the following PTs and subgroups had an increased disproportional reporting value (EB05 \geq 2) for the Pfizer-BioNTech COVID-19 Vaccine (Table 2):

Table 2: Preferred Terms with Disproportional Reporting in Empirica Signal for the Pfizer-BioNTech COVID-19 Vaccine

Preferred Term (PT)	U.S. EB05	U.S. Infant (0-23.9 months) EB05	U.S. Adult \geq 65 years EB05	U.S. Female EB05
Body height			2.17	
Disease recurrence	2.05			
Drug ineffective	2.29			
Exposure via breast milk		17.41		
Immunisation			2.24	
Investigation	2.16		2.25	2.04
Product preparation issue			2.18	
Weight	2.02		2.13	

Reviewer comment: There were no PTs with disproportionate reporting among children (age 2-8.9 years) or teens (standard Empirica run for ages 9-18.9 years). Review of PTs with an EB05 \geq 2 did not identify new safety concerns.

Reports concerning the PTs “body height” and “weight” generally refer to patient body measurements provided in VAERS reports or changes in weight/height. The PT “investigation” is non-specific and generally refers to investigations performed as part of a work-up for signs or symptoms and does not represent an adverse event. Similarly, the PT “immunisation” refers to the patient having been immunized and does not represent an adverse event. The PT “product preparation issue” generally concerns reports with issues such as incorrect vaccine reconstitution or lack of reconstitution with diluent and may not be associated with an adverse event.

¹ Empirica Signal is a web-based platform that uses an automated approach to explore relationships in large datasets by generating statistical scores for combinations of products and events from drug or vaccine databases. Data mining is conducted to evaluate whether any events (i.e., MedDRA PTs) following use of a particular vaccine are disproportionately reported compared to all vaccine reports in VAERS; the threshold for signal detection is an EB05 value \geq 2. (EB05 is the lower bound of the 90% confidence limit for the Empirical Bayesian Geometric Mean). The data generated from Empirica Signal do not, by themselves, demonstrate causal associations, but the data might serve as a signal for further investigation and can be useful for hypothesis generation and exploration of potential concerns.

A cumulative VAERS query run on March 10, 2022 for “disease recurrence” following the Pfizer-BioNTech COVID-19 Vaccine returned 2,647 total reports (289 U.S. reports). Among the 289 U.S. reports, 147 (50.9%) were non-fatal serious reports and 3 (1.0%) were death reports. Three U.S. reports (all non-fatal serious) concerned individuals 12-15 years of age. One report was regarding a 12-year-old male with a history of atrial fibrillation and AV node ablation procedure who experienced recurrence of heart rhythm irregularity that began 9-days post-2nd dose and was treated with metoprolol. Another report concerned a 12-year-old female with “generally well-controlled epilepsy” (last seizure 2020) who experienced status epilepticus starting 31 hours post-2nd dose; the individual had symptoms of headache, fatigue, myalgias, and chills for approximately 16 hours before seizures began and was febrile to 101°F at time of arrival to the hospital. The third report was regarding a 13-year-old male with a history of epistaxis who experienced epistaxis, dizziness, and headache the same day post-1st dose.

Use of the product during pregnancy and lactation is considered an area of “missing information” in the PVP that will additionally be monitored through post-authorization safety studies, including a PMC Pregnancy Registry study. Review of VAERS data has not suggested patterns concerning for safety issues during pregnancy and lactation. Vaccine effectiveness is also an area considered as “missing information” in the PVP and is monitored through clinical trials, and post-authorization studies conducted by the sponsor.

7 Pharmacovigilance Plan

7.1 Summary of Pharmacovigilance Plan

The sponsor submitted a revised PVP (Version 1.4.1) which continues to include routine pharmacovigilance, risk communication, and postmarketing observational and active surveillance safety studies (Table 3). There are also ongoing clinical trials.

Table 3: Summary of Safety Concerns and Planned Pharmacovigilance Activities*

Safety Concern	Actions Proposed
Important Identified Risks	
Anaphylaxis	<ul style="list-style-type: none"> • Communication of this important identified risk via label (Sections 4 - Contraindications, 5.1 - Management of Acute Allergic Reactions, Section 6.2 – Postmarketing Experience). • C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. • C4591009: A non-interventional post-approval

	<p>safety study of the Pfizer--BioNTech COVID-19 vaccine in the United States.</p> <ul style="list-style-type: none"> • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the U.S. Department of Defense population following Emergency Use Authorization. • C4591012: 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. • C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.
Myocarditis and Pericarditis	<ul style="list-style-type: none"> • Communication of this important identified risk via label (Section 5.2 - Myocarditis and Pericarditis, Section 6.2 - Postmarketing Experience). • C4591009: A non-interventional post-approval safety study of the Pfizer—BioNTech COVID-19 vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the U.S. Department of Defense population following Emergency Use Authorization. • C4591012: 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. • C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. • C4591038 (formerly C4591021 substudy): Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine. Substudy to investigate natural history of post-vaccination myocarditis and pericarditis. • C4591036: Pediatric Heart Network Study: Low interventional cohort study of myocarditis associated with Comirnaty in persons less than 21 years of age. • C4591031 substudy B: A randomized, placebo-

	<p>controlled, observer-blind cross-over substudy to evaluate the safety and tolerability of a booster (third) dose of BNT162b2. Participants ≥ 12 years of age to ≤ 30 years of age who have completed a 2-dose primary series of BNT162b2 (30 mcg doses) at least 6 months (≥ 12 months for those 12-17 years of age) prior to randomization will be enrolled.</p> <ul style="list-style-type: none"> • C4591007 substudy – Troponin group: A Phase 3 substudy of 750 participants 5 to < 12 years of age (randomized 2:1 to receive BNT162b2 10 μg or placebo) and 500 participants 12-< 16 years of age (open label receipt of BNT162b2 30 μg).
Important Potential Risks	
<p>Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)</p>	<ul style="list-style-type: none"> • C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. • C4591008: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in U.S. healthcare workers, their families, and their communities. • C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer--BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization. • C4591012: 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. • C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.
Missing Information	
<p>Use in pregnancy and lactation</p>	<ul style="list-style-type: none"> • C4591015: A phase 2/3, placebo-controlled, randomized, observer blind study to evaluate the

	<p>safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older.</p> <ul style="list-style-type: none"> • C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 vaccine in the United States. • C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the U.S. Department of Defense population following Emergency Use Authorization. • C4591021: Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. • C4591022: 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.
<p>Vaccine effectiveness</p>	<ul style="list-style-type: none"> • C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California. • W1235284: Determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization. COVID-19 Amendment for COVID VE/ Sub-study 6. • W1255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance Study. • BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses. • C4591007 substudy – Lower dose evaluation group: To study lower dose levels of BNT162b2 in individuals 12 through <18 years of age.
<p>Use in pediatric individuals <5 years of age</p>	<p>Actions proposed in the PVP that are inclusive of individuals <5 years of age include†:</p> <ul style="list-style-type: none"> • C4591007: Lower dose evaluation group:

	<p>Phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and Phase 2/3 placebo-controlled, observer blinded safety, tolerability, and immunogenicity, study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children <12 years of age.</p> <ul style="list-style-type: none"> • C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 Vaccine in the United States. • C4591021/ C4591038 (C4591021 substudy): Post Conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. Substudy to investigate natural history of post-vaccination myocarditis and pericarditis. • C4591023: Phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy infants <6 months of age. • C4591036: Pediatric Heart Network Study: Low interventional cohort study of myocarditis associated with Comirnaty in persons less than 21 years of age.
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*Adapted from sponsor’s Pharmacovigilance Plan, Version 1.4.1, Tables 52-57.

†Clinical trials (i.e., C4591001) that were originally included in the PVP to address missing information on “Use in pediatric individuals <16 years of age” are also included in the PVP.

7.2 Summary of Post-Approval Safety Surveillance Studies

The sponsor’s proposed post-approval safety surveillance studies are briefly summarized in the sections below. In addition to PMR studies for myocarditis/pericarditis included in the BLA 125742/0 approval letter, there were PMC studies, including a pregnancy registry study (PMC #10, C4591022) and an active safety surveillance study in the Veteran’s Affairs Health System (PMC #12, C4591012). The Sponsor also plans to conduct a vaccine effectiveness Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser

Permanente Southern California” (PMC #13). Please see the previous BLA (125742) and EUA (27034) PVP review memos for additional details.

Reviewer comment: The pregnancy registry study (PMC #10, C4591022) includes pregnant individuals aged 18 years and older. An IR was sent asking the sponsor to include pregnant individuals of all ages in the study. The sponsor’s IR response (125742/45/10) indicated that the pregnancy registry study protocol will be revised to include pregnant individuals of all ages. The sponsor noted that the target enrollment sample size has been met in the exposed group of pregnant individuals who received Pfizer-BioNTech COVID-19 Vaccine, however, they will attempt to enroll individuals <18 years of age who may qualify for this group. An amended study protocol and statistical analysis plan (SAP) will be submitted by May 20, 2022. Study C4591012 (PMC #12, Veteran’s Affairs Health System study) includes various age subgroups, including 12- <18 years, although the focus is on the elderly. Study C4591014 (PMC #13, vaccine effectiveness study) includes all Kaiser Permanente Southern California members meeting vaccination eligibility to allow analyses based on evolving age requirements.

Studies Included in BLA Approval Letter (125742/0) as Postmarketing Requirements (PMRs) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA)

The sponsor is required to conduct the following studies under BLA approval of Comirnaty to assess the known serious risks of myocarditis and pericarditis and to identify an unexpected serious risk of subclinical myocarditis.

PMR #4, C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States

Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general U.S. population of all ages, pregnant women, the immunocompromised, and persons with a prior history of COVID-19 within selected data sources participating in the U.S. Sentinel System.

Study milestones in BLA (125742/0) approval letter:

Final protocol submission: August 31, 2021
Monitoring report submission: October 31, 2022
Interim report submission: October 31, 2023
Study completion: June 30, 2025
Final study report submission: October 31, 2025

Reviewer comment: A final study protocol was submitted on August 30, 2021 (IND 19736.470 and EUA 27034.283). A protocol amendment was submitted on December 23, 2021 (IND 19736.617) which specified myocarditis/pericarditis as safety events of interest in the primary study objectives and included assessment of safety events following a third/booster dose of the Pfizer-BioNTech COVID-19 Vaccine. While this study includes individuals of all ages, including those aged 12-15 years, the protocol

indicates that safety analyses will be limited to individuals within the age-approved population for Pfizer-BioNTech COVID-19 Vaccine with age-based eligibility criteria changing over the study period as the ages approved for vaccine use change.

PMR #5, C4591021: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Objective: To assess the potential increased risk of adverse events of special interest (AESI), including myocarditis and pericarditis, after being vaccinated with at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

Study milestones in BLA (125742/0) approval letter:

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

Reviewer comment: The final study protocol was submitted (BLA 125742.0.42 and IND 19336.464) and reviewed. A protocol amendment and SAP were received (IND 19736.619) on December 23, 2021 and have been reviewed. The protocol amendment includes the addition of myocarditis/pericarditis as outcomes separate from the cardiovascular composite endpoint, a sensitivity analysis to assess AESIs after 2nd and 3rd vaccine doses, and additional stratification of the 0-19 years age group. The study source population will include all individuals registered in each of the healthcare data sources who are eligible to receive the Pfizer-BioNTech COVID-19 Vaccine. This study is being conducted in Europe and vaccine eligibility will depend on European vaccine eligibility criteria.

PMR #6, C4591021 Substudy (currently referred to as Study C4591038): Substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

Objective: To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within one year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.

Study milestones in BLA (125742/0) approval letter:

Final Protocol Submission: January 31, 2022

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

Reviewer comment: This natural history substudy is being conducted in Europe and vaccine eligibility will depend on European vaccine eligibility criteria. A final study protocol was submitted on January 31, 2022 (IND 19736.656) and has been reviewed. The protocol includes an age category for individuals aged 0-17 years, including a subgroup for individuals aged 12-15 years (where feasible).

PMR #7, C4591036: 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 [PHN]).

Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.

Study milestones in BLA (125742/0) approval letter:

Final Protocol Submission: November 30, 2021

Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

Reviewer comment: This study includes individuals <21 years of age and is inclusive of the population proposed for vaccine use in this BLA supplement. A final study protocol was received on November 29, 2021 (IND 19736.579) and has been reviewed.

PMR #8, C4591007 Substudy: 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.

Objective: To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing in order to evaluate the frequency of subclinical myocarditis amongst individuals 5 to 15 years of age.

Study milestones in BLA (125742/0) approval letter:

Final Protocol Submission: September 30, 2021

Study Completion: November 30, 2023

Final Report Submission: May 31, 2024

Reviewer comment: This substudy includes participants in the age range of the proposed BLA supplement (i.e., individuals 12-15 years of age) who are currently able to receive vaccine under EUA. OBPV defers review of this study to OVR.

PMR #9, C4591031 substudy: 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.

Objective: To obtain serum samples within the first ~4 days after vaccination for potential Troponin I testing in order to evaluate the frequency of subclinical myocarditis amongst individuals 12 to 30 years of age following a third/booster vaccine dose.

Study milestones in BLA (125742/0) approval letter:

Final Protocol Submission: November 30, 2021

Study Completion: June 30, 2022

Final Report Submission: December 31, 2022

Reviewer comment: The original BLA approval letter indicated this study would include participants aged 16 to 30 years of age. The current PVP indicates this substudy has expanded the lower age range of participants to 12 years of age, consistent with the proposed indication for this BLA supplement. OBPV defers review of this study to OVR.

8 DE Assessment of Sponsor's Pharmacovigilance Plan

This PVP assessment is focused on use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age. Please see the original BLA PVP review memo and PVP addendum memo for additional details.

8.1 Important Identified Risk: Anaphylaxis

There were no reports of anaphylaxis following receipt of BNT162b2 in Study C4591001 among individuals 12-15 years of age during the blinded placebo-controlled period. Review of the sponsor's data from their safety database through September 30, 2021 showed 43 (1.3%; 8 U.S.) reports of anaphylactic reaction/shock or anaphylactoid reaction/shock among individuals 12-15 years of age; all were serious events, and none were fatal. The majority (n=37, 86.0%) of anaphylaxis/anaphylactoid events occurred <24 hours after vaccination. A search of VAERS data (cumulative query run March 9, 2022) revealed 43 total U.S. reports among individuals aged 12-15 years, including 14 non-fatal serious/OMIC reports (no death reports).

The important identified risk of anaphylaxis, which can be fatal or life-threatening, will be monitored through passive AE reporting and postmarketing safety studies. This safety concern is labeled in the following sections of the label:

- Section 4 Contraindications

- Section 5 Warnings and Precautions, 5.1 Management of Acute Allergic Reactions
- Section 6.2 Postmarketing Experience

Reviewer comment: The proposed PVP is acceptable to monitor the risk of anaphylaxis.

8.2 Important Identified Risk: Myocarditis and Pericarditis

There was one SAE of myocarditis in Study C4591001 which occurred in a 16-year-old male who experienced chest pain on Day 3 after Dose 4 (2nd dose BNT162b2). This individual had a history one week prior of fever, cough, rhinorrhea, and positive PCR for rhinovirus from a respiratory virus panel (SARS-CoV-2 RNA PCR was negative). His chest pain resolved within 24-hours of receiving ketorolac and he was discharged home after 2-days of hospitalization. Through September 30, 2021, there were 180 reports of myocarditis and pericarditis retrieved from the sponsor's safety database among individuals 12-15 years of age, including 154 reports (26 U.S.) of myocarditis and 61 reports (4 U.S.) of pericarditis (35 reports involved patients with both myocarditis and pericarditis); none had a fatal outcome. A VAERS search for U.S. reports among individuals aged 12-15 years revealed 528 reports, including 445 (84.2%) serious and 5 (0.9%) death reports for 4 unique individuals (described in Section 6.1; cumulative query run March 9, 2022).

Monitoring for myocarditis and pericarditis is ongoing and includes the following activities:

- Continued passive surveillance using VAERS
- Vaccine Safety Datalink (VSD) analyses for safety signals
- Ongoing Sponsor passive surveillance using worldwide adverse events data
- Ongoing Sponsor voluntary surveillance studies

In addition, the approval letter for Comirnaty (125742/0) includes PMR safety studies under FDAAA Title IX to further characterize the serious risks of myocarditis and pericarditis. This safety concern is labeled in the following sections of the label:

- Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis
- Section 6.2 Postmarketing Experience

Reviewer comment: The sponsor's proposed PVP and FDA required postmarketing studies are acceptable to monitor and further assess the risk of myocarditis and pericarditis including long-term follow up.

8.3 Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

No reports of VAED/VAERD have been identified in Study C4591001 or through post-authorization surveillance among individuals 12-15 years of age. The important potential

risk of VAED will be monitored through passive AE reporting and postmarketing safety studies.

Reviewer comment: The proposed PVP is acceptable to monitor the potential risk of VAED and VAERD.

8.4 Missing Information: Use in pregnancy and lactation

Pregnant women were excluded from the pivotal clinical trial; non-interventional post-authorization studies to assess use of BNT162b2 in pregnancy are planned or ongoing. There were no known pregnant or breastfeeding individuals in the Study C4591001 among participants 12-15 years of age. Missing information regarding the use of the product during pregnancy and lactation will be monitored through passive AE reporting, a clinical trial, and postmarketing safety studies, including a PMC Pregnancy Registry study. Use in pregnancy and lactation will be communicated in product labeling (Section 8.1 Pregnancy and 8.2 Lactation), including a link to enroll in the pregnancy registry.

Reviewer comment: CDC recommends COVID-19 vaccination for people who are pregnant, breastfeeding, or trying to get pregnant now, or might become pregnant in the future.⁴ CDC further states that evidence continues to build showing that COVID-19 vaccination before and during pregnancy is safe and effective and that data on the safety of receiving an mRNA COVID-19 vaccine, Moderna or Pfizer-BioNTech (Comirnaty), during pregnancy are reassuring.⁴ Early data from three safety monitoring systems (i.e., v-safe surveillance system, v-safe pregnancy registry, and VAERS) did not find any safety concerns for people who received an mRNA COVID-19 vaccine late in pregnancy or for their babies.^{4,5} Monitoring of COVID-19 vaccination during pregnancy and lactation is ongoing. The proposed PVP is acceptable to monitor for use in pregnancy and lactation.

8.5 Missing Information: Vaccine effectiveness

The real-world vaccine effectiveness of the Pfizer-BioNTech COVID-19 Vaccine outside of clinical trials and over the course of the SARS-CoV-2 pandemic in larger and more diverse populations continues to evolve. Missing information regarding real-world vaccine effectiveness will be monitored through postmarketing real-world vaccine effectiveness studies. Data on vaccine efficacy in clinical trials will be communicated in product labeling (Section 14 Clinical Studies).

Reviewer comment: Study C4591014 (PMC #13) entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California” is being conducted to evaluate vaccine effectiveness outside of clinical trials. The proposed PVP to monitor vaccine effectiveness is acceptable.

8.6 Missing Information: Use in pediatric individuals <5 years of age

Use of BNT162b2 in pediatric individuals <5 years of age is being evaluated in clinical trials. Among individuals <5 years of age, cumulative post-authorization data from the sponsor's safety database identified 56 reports (13 U.S. reports) including 14 serious reports; two reports included fatal outcomes (see Section 5.3 of this memo). Missing information regarding pediatric individuals <5 years of age will be monitored through passive AE reporting and post-authorization/postmarketing safety studies. The lack of safety data will be communicated in product labeling (Section 8.4 Pediatric Use).

Reviewer comment: The proposed PVP is acceptable to monitor use in individuals <5 years of age.

9 DPV Conclusions

Based on review of available data, there were no new safety signals among participants 12-15 years of age who received BNT162b2 in Study C4591001. Review of the sponsor's post-authorization safety data, VAERS data, and data mining findings did not reveal new safety concerns among individuals 12-15 years of age.

The sponsor will conduct routine pharmacovigilance and postmarketing observational studies, which were previously identified in the August 23, 2021 approval letter for Comirnaty BLA 125742/0 as FDAAA Title IX PMR safety studies (PMRs# 4 – 7) to assess the known serious risks of myocarditis and pericarditis. Also, the sponsor will conduct PMC studies, including a pregnancy registry study (PMC #10, C4591022) and an active safety surveillance study in the Veteran's Affairs Health System (PMC #12, C4591012). Furthermore, the sponsor will assess vaccine effectiveness in Study C4591014 (PMC #13) entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California." In addition, the safety of BNT162b2 in individuals 12-15 years of age can be communicated through labeling.

10 DPV Recommendations

Should the product be approved in individuals 12-15 years of age, based on the review of the clinical trial safety data, and the post-authorization safety data, OBPV/DPV recommends the following actions:

- **Routine pharmacovigilance** in accordance with adverse event reporting regulations under 21 CFR 600.80, as per the sponsor's revised PVP. Additionally, following approval of Comirnaty 125742/0, the sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.

- **Postmarketing requirement (PMR) safety studies** under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to assess the serious risk of myocarditis and pericarditis, as outlined in the BLA 125742/0 approval letter.
- **Postmarketing commitment (PMC) safety studies**, including a pregnancy registry (C4591022) to assess whether pregnant women receiving the Pfizer-BioNTech COVID-19 Vaccine experience an increased risk of pregnancy and infant safety outcomes compared to comparator groups.
- **Voluntary postmarketing studies:** Post-EUA studies that continue as voluntary studies will be followed through updates in periodic safety update reports (PSURs).

At this time, the available safety data do not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy (REMS). Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

References

1. Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:283–288. DOI: <http://dx.doi.org/10.15585/mmwr.mm7008e3>
2. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:46–51. DOI: <http://dx.doi.org/10.15585/mmwr.mm7002e1>
3. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868-878. doi:10.1016/j.jaci.2015.07.048
4. COVID-19 Vaccines While Pregnant or Breastfeeding. Available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html#anchor_1628692520287; Accessed on April 21, 2022.
5. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons [published correction appears in *N Engl J Med*. 2021 Oct 14;385(16):1536]. *N Engl J Med*. 2021;384(24):2273-2282. doi:10.1056/NEJMoa2104983