



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

PHARMACOVIGILANCE EUA MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: Pfizer

Product: Pfizer-BioNTech COVID-19 Vaccine*

Application Type/Number: EUA 27034

Proposed Indication: Active immunization to prevent COVID-19 in
individuals 16 years of age or older

Submission Date: November 20, 2020

Action Due Date: December 14, 2020

*The product was also referred to as BNT162b2 in the clinical development

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the plan for active surveillance and pharmacovigilance activities based on the safety profile of Pfizer-BioNTech COVID-19 Vaccine.

2 PRODUCT INFORMATION

2.1 Product Description

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

The product is administered as a series of two doses (0.3 mL) each 21 days apart by intramuscular injection.

2.2 Proposed indication

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

3 PERTINENT REGULATORY HISTORY

On December 2, 2020, the product was authorized in United Kingdom. On December 9, 2020, in response to cases of possible anaphylaxis occurring during their mass vaccination efforts, UK regulators issued a guidance stating that the vaccine should not be given to any person with a history of a significant allergic reaction to a vaccine, medicine, or food. In addition, they advised resuscitation facilities should be available at all times for all vaccinations.

The Sponsor submitted a rolling Marketing Authorization Application on October 5, 2020 to the European Medicines Agency. Feedback on pharmacovigilance methods and active surveillance plans was provided in IND19736.84, IND19736.91, IND19736.113, IND19736.121, and IND19736.125.

4 DESCRIPTION OF PRODUCT SAFETY DATABASE

4.1 Clinical studies

Two studies were conducted, BNT162-01 and C4591001. **Table 1** below provides a summary of these studies.

Table 1. Summary of clinical studies supporting the safety and efficacy of Pfizer-BioNTech COVID-19 vaccine*‡

Study	Description	N
BNT162-01	Phase 1/2 randomized, open-label, dose-escalation, first in-human study of BNT162b2 in adults 18 - 55 years of age. BNT162b2 was evaluated at five dose levels (1, 3, 10, 20, 30 µg)	60
C4591001	<p>Phase 1/2/3 randomized, observer-blind, placebo control</p> <p>Phase 1: Adults 18 - 55, and 65 - 85 years of age. BNT162b2 was evaluated at three dose levels (10, 20, 30 µg), or placebo</p> <p>Phase 2: Adults 18 - 55, and 65 - 85 years of age. Subjects were given 30 µg BNT162b2 or placebo.</p> <p>Phase 3: Adolescents and adults 12 - 15, 16 - 55, and > 55 years of age</p>	<p>Phase 1: 90 randomized 4:1 within each dose/age group</p> <p>Phase 2: 360 randomized 1:1</p> <p>Phase 3: ~44,000 randomized 1:1 (includes 360 subjects from Phase 2)</p>

*Adapted from Table 5, EUA Request for Pfizer-BioNTech COVID-19 Vaccine, EUA27034, Module 1.19

‡ BNT162-01 evaluated four vaccine candidates; Phase 1 of C4591001 evaluated two vaccine candidates. The numbers in this table reflect subjects administered BNT162b2.

BNT162-01

BNT162-01 was a dose-finding Phase 1/2 study not conducted under a U.S. IND that evaluated four candidate vaccines in healthy adults 18 to 55 years of age. For each vaccine candidate, subjects received escalating dose levels (n = 12 per dose level) with progression to subsequent dose levels based on recommendations from a Sponsor Safety Review Committee.

Participants were asked to record local reactions, systemic events, and antipyretic or pain medication use for seven days each evening in a paper diary after administration of the study product. Treatment-emergent adverse events (AEs) were recorded up to one month following the second dose and assessed for seriousness and relationship to the study vaccine. AEs of special interest (AESIs) included enhanced respiratory disease or flu-like symptoms that did not resolve after seven days.

C4591001

The Sponsor selected two candidate vaccines, BNT162b1 and BNT162b2, for further investigation in Study C4591001 based on the data from Study BNT162-01. Study C4591001 was a Phase 1/2/3 randomized, placebo-controlled, observer-blinded, vaccine candidate selection, dose-finding study in healthy adults that studied two potential vaccine candidates. Multiple dose levels of the two vaccine candidates were studied using a two-dose schedule given 21 days apart. Age cohorts initially evaluated were 18 to 55 years, and 65 to 85 years. BNT162b2 at a 30 µg dose was selected for further study in a Phase 2/3 expanded cohort based on a more favorable reactogenicity profile, and a trend towards earlier clearance of the product in a nonhuman primate challenge study. Phase 2 of Study C4591001 has completed enrollment, consisting of 180 subjects that were given vaccine and 180 subjects administered placebo. Phase 3 of the study is ongoing, and added the enrollment of adolescents 16 to 17 years of age and 12 to ≤ 16 years.

All phase 1 participants and a subset of Phase 2/3 participants recorded local reactions, systemic events, and antipyretic/pain medication use through Day 7 after each dose. The reactogenicity assessments included solicited assessment of injection site reactions such as pain, redness, or swelling, as well as systemic AEs that included fever, fatigue, chills, headache, vomiting, diarrhea, muscle or joint pain. Phase 2/3 participants not in the reactogenicity subset that had local reactions and systemic events consistent with reactogenicity detected were reported as unsolicited AEs. Unsolicited AEs from all participants were collected from Dose 1 to one month after the last dose, and serious adverse events (SAEs) from Dose 1 to 6 months after the last dose. Participants will be followed for 24 months.

4.2 Adverse events

In general, adverse events occurred more frequently in vaccinated subjects compared to placebo subjects. The increased number of AEs in vaccinated groups was largely due to reactogenicity seven days after vaccination. For all age groups, pain at the injection site was the most common solicited local AE and was more common in younger subjects. Solicited systemic AEs that were more common in the vaccinated group compared to placebo include fever, fatigue, headache, chills, muscle or joint pain; the frequency and severity of solicited systemic AEs were higher in younger age groups and with Dose 2.

Unsolicited, non-serious, AEs occurred more frequently in the vaccine group compared to placebo and were mainly attributed to AEs consistent with reactogenicity. Lymphadenopathy was more common in the vaccine group compared to placebo, which may plausibly be related to vaccine. There were four cases of Bell's palsy in the vaccine group; these cases occurred 3, 9, and 48 days after Dose 2 and on day 37 after Dose 1. There were no other imbalances noted between the vaccine and placebo group for non-serious AEs.

Reviewer comment: A total of four cases of Bell's palsy were identified in the response to the IR dated December 4, 2020 (EUA27034/0.12), all of which were in the vaccine group. The annual incidence rate of Bell's palsy is approximately 15 - 30 cases per 100,000 population (1-3), which translates to an approximate expected incidence of 2 cases per 10,000 subjects. Based on this, one would expect approximately 4 cases in a population of 22,000. Thus, the number of cases of Bell's palsy is not higher than expected given the background rate.

The frequency of subjects who reported at least one SAE in the overall safety database was 0.6% in the BNT162b2 group and 0.5% in the placebo group. The most frequently reported SAEs were in the Cardiac Disorders SOC (0.1% in each treatment group), Nervous System Disorders SOC (0.1% in each treatment group), and Infections and Infestations SOC (0.1% in each treatment group). There were 12 participants with appendicitis, 8 of which were in the BNT162b2 group and 4 in the placebo group.

Reviewer comment: The incidence of appendicitis depends upon the population studied (4-7), but is estimated at 100 cases per 100,000 in North America (6) or 10 cases per 10,000 subjects per year. Based on this, one would expect approximately 22 cases in a population of 22,000 vaccinees. Thus, the number of cases of appendicitis is not higher than expected given the background rate. Additionally, the cases in the vaccination group occurred in younger participants (ages 19 - 63, median age 40) who have a higher rate of appendicitis (4-7).

There were six subjects, all in Phase 3, who died up to the DLP of November 14, 2020. Two participants who died were in the vaccine group, and 4 were in the placebo group. Brief case narratives for the patients who died include:

- A 60 year old male in the BNT162b2 group with a history of obesity, traumatic brain injury, depression, and hip replacement was found dead in his home three days after dose 1. The probable cause of death according to the medical examiner was progression of atherosclerotic disease, although the complete autopsy report is pending.
- A 56 year old female with a past medical history of obesity, sleep apnea, and supraventricular tachycardia in the BNT162b2 group experienced a SAE of cardiac arrest and died 62 days after Dose 2. SARS Co-V-2 test was negative.
- A 42 year old female in the placebo group with a history of recurrent breast cancer was found dead the day after a normal evening. Death occurred 8 days after dose 1. Autopsy was performed and results are pending.
- A 61 year old female in the placebo group with a history of hypertension was diagnosed with hemorrhagic stroke 14 days after dose 2. The patient died the next day.
- A 51 year old female in the placebo group with a medical history of hypothyroidism, chronic obstructive pulmonary disease, hypertension, and osteoarthritis was found deceased in her home 34 days after dose 2. An autopsy was not performed and the cause of death was unknown. The patient complained of "stomach pain" to family members three days prior to being found deceased in her home.

- A 58 year old male with a past medical history of hypertension, gastroesophageal reflux disease, hyponatremia, seizures, alcohol abuse, myocardial infarction, and cardiomyopathy in the placebo group experienced a SAE of myocardial infarction 15 days after dose 1 and died the same day.

There were 10 severe COVID-19 cases that occurred after Dose 1. Nine of these severe COVID-19 cases were in the placebo group and one was in the BNT162b2 group. The subject in the BNT162b2 group was a 41 year old female in Brazil with a past medical history of headache and congenital osteodystrophy. The subject was diagnosed with COVID-19 and reported new loss of taste or smell, cough, sore throat, and rhinitis with symptoms beginning 35 days after receiving dose 2. The subject had an oxygen saturation of 93% on room air. The subject was considered a case of severe COVID-19 illness per the study protocol due to confirmed COVID-19 and oxygen saturation $\leq 93\%$. The report does not indicate whether the patient was hospitalized or received supplemental oxygen therapy.

As of the DLP, 23 subjects reported pregnancies, 12 of which were in the vaccine group and 11 in the placebo. AEs related to pregnancy were spontaneous abortion and retained products of conception, both in the placebo group. Participants are being monitored for pregnancy outcomes.

5 SPONSOR'S PHARMACOVIGILANCE PLAN (PVP)

A summary of the Sponsor's pharmacovigilance plan (PVP) is provided in **Table 2** below which describes the important potential risks and missing information for Pfizer-BioNTech COVID-19 vaccine. The Sponsor will conduct both passive and active surveillance activities for the safety concerns listed below.

Table 2 Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Identified	The Sponsor does not include any Important Identified Risks.	Not applicable
Potential	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	<ul style="list-style-type: none"> ▪ Pharmacovigilance ▪ Mandatory reporting of cases of COVID-19 that result in hospitalization or death ▪ Data capture aid ▪ Completion of the Phase 1/2/3 randomized, placebo-controlled study evaluating safety and efficacy with surveillance for two years following dose 2 ▪ Three post-authorization safety studies to perform long-term active surveillance for

		safety events of interest among subjects administered Pfizer-BioNTech COVID-19 vaccine
Missing	Use in pregnancy and lactation	<ul style="list-style-type: none"> ▪ Pharmacovigilance ▪ Planned post-licensure clinical study to assess safety and immunogenicity in pregnant women ▪ Active surveillance studies to monitor vaccine-exposed pregnancies under EUA within the U.S.
Missing	Vaccine effectiveness	<ul style="list-style-type: none"> ▪ Pharmacovigilance ▪ Mandatory reporting of cases of COVID-19 that result in hospitalization or death ▪ Data capture aid ▪ Non-interventional study of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting ▪ Immunogenicity study in immunocompromised subjects, including assessment of antibody and cell-mediated responses
Missing	Use in pediatric individuals < 16 years of age	<ul style="list-style-type: none"> ▪ Pharmacovigilance ▪ ≥ 12 to ≤15 years: Phase 1/2/3 randomized, placebo-controlled study (C4591001) ▪ 5 to < 12 years: Phase 1 open label dose-finding study in healthy children and adolescents (C4591007) ▪ 0 to < 5 years: Phase 1 open label dose-finding study in healthy toddlers, infants, and children 0 to < 5 years old (Protocol number not assigned)

*Adapted from Tables 22 - 26, Pharmacovigilance Plan for Emergency Use Authorization 27034, EUA27034/0.15, Module 1.16.1; Section 13 of the EUA document, Module 1.19.1

The Sponsor plans to use a data capture aid (DCA) to characterize the important potential risk of VAED/VAERD and the missing information of vaccine effectiveness identified in their PVP. The DCA will obtain follow-up information in a structured manner

for cases of COVID-19 disease following the Pfizer-BioNTech COVID-19 vaccine and has fields for the type of vaccine administered, number and timing of doses, the time between vaccination and COVID-19 disease, and disease severity. The Sponsor will also use a web-based AE reporting portal that will be available to vaccine providers and recipients for capturing AE data with automated intake into the Sponsor safety database via a standardized format for safety review.

The Sponsor plans pharmacovigilance including collection and reporting of AEs to the Vaccine Adverse Event Reporting System (VAERS). The EUA will require the Sponsor to report the following events to VAERS within 15 days:

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

The EUA will require submission of monthly periodic safety reports containing descriptive information which includes:

- a) A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- b) Newly identified safety concerns in the interval
- c) Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

The Sponsor will conduct one or more post-authorization epidemiologic study(ies) for active follow-up for safety (including deaths and hospitalizations, adverse events of special interest, vaccination during pregnancy, and other clinically significant events of interest) among individuals administered the Pfizer-BioNTech COVID-19 Vaccine during EUA. This study or studies should include: active query and follow-up of a large sample of recipients receiving the vaccine under EUA, and/or an analysis of a large population of healthcare recipients (e.g., via healthcare service claims database or electronic medical records) to identify these AEs. This study(ies) should include a follow-up period of at least one year after vaccination and include comparisons to AESI rates in an unvaccinated or other suitable comparison population.

Mandatory reporting by vaccination providers

Vaccination providers will also be required to report AEs and vaccination administration errors to VAERS. The EUA will require reporting of:

- Vaccination administration errors, whether or not associated with an AE
- SAEs, irrespective of attribution to vaccination
- Cases of Multisystem Inflammatory Syndrome (MIS)

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

Additional VAERS Reporting

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

5.1 Post-authorization active surveillance studies

The Sponsor proposes three studies to evaluate safety in persons in the U.S. receiving the vaccine, and to estimate the incidence rate of AESIs over a 30-month period following vaccine availability under the EUA.

5.1.1 Post-Emergency Use Authorization Observational Cohort Study to Evaluate the Safety of SARS-COV-2 RNA Vaccine in Healthcare Workers: A primary data collection active surveillance study (Study Protocol C4591008)

The Sponsor proposes this study to evaluate the rates of adverse events of interest and other clinically significant events of interest among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a cohort of U.S. healthcare workers, and to compare these rates to expected rates. The objectives of the study are:

Primary Objectives

- Estimate the real-world incidence of Adverse Events of Special Interest (AESI), such as vaccine enhanced disease, which is potentially indicated by unexpected patterns of serious COVID-19 illness, and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine beginning with an EUA in a cohort of U.S. healthcare workers.
- Characterize the utilization patterns of vaccine among healthcare workers, including estimating the proportion of participants in the underlying HERO registry receiving vaccine, the completion and timing of the dosing schedule, and the demographics and health histories of recipients

Secondary Objectives

- Evaluate whether the vaccine recipients experience increased risk of AESI and other clinically significant events post-vaccination.
- Estimate the incidence rates of AESI and clinically significant events among subcohorts of interest such as women of childbearing age, immunocompromised people, and stratifications by age.

- Characterize utilization patterns of vaccine in subcohorts of interest such as women of childbearing age, immunocompromised, and within different age categories.

The study will enroll approximately 20,000 vaccinated healthcare workers that will be followed-up to 30-months with periodic surveys on their health. Healthcare workers will be recruited from the Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, and health systems distributing the Pfizer-BioNTech COVID-19 vaccine to its employees.

Participants can self-enroll remotely or in person at the vaccination site. Study navigators will assist with entry of vaccine-related information such as manufacturer, lot number, and dates of administration. After enrollment, participants will enter data into a web-portal at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 6 months, 9 months, 12 months, 18 months, 24 months, and 30 months. Participants will be queried for second dose information, their general health, and events needing medical attention. Medical records and insurance claims will be requested and reviewed for subjects who report clinically important medical events such as a non-routine visit to a healthcare provider, hospitalization, or missing work due to illness. A Clinical Event Ascertainment group, which will include infectious disease and cardiologist physicians, will adjudicate medical records to confirm events for inclusion in the primary analysis. Medical records during the year prior to vaccination may also be reviewed to support a self-controlled case series analysis. Subjects who do not complete data entry within a certain period of time will be contacted by a centralized call center.

The following are considered AESI in this study: acute disseminated encephalomyelitis; anaphylaxis; acute myocardial infarction; myocarditis/pericarditis; stroke; death; pregnancy and birth outcomes; other acute demyelinating diseases; Multisystem Inflammatory Syndrome in children; vaccine enhanced disease; disseminated intravascular coagulation; venous thromboembolism; Kawasaki disease; convulsions/seizures; Guillain-Barré syndrome; transverse myelitis; encephalitis/myelitis/encephalomyelitis/meningoencephalitis/meningitis/encephalopathy; narcolepsy and cataplexy; non-anaphylactic allergic reactions; thrombocytopenia; and arthritis and arthralgia/joint pain.

AESI and other clinically significant event rates will be represented using incidence rates with confidence intervals. Stratification variables may include healthcare worker role, work setting, age, health status, and geographic region. To evaluate whether vaccinated persons experience increased risk of AESIs or clinically relevant events, a self-controlled case series analysis will be conducted to compare event frequency within the risk period to the frequency in the control period.

The proposed milestones are:

- Final protocol submission: December 31, 2020
- Study completion date: June 30, 2023
- Final report submission: December 31, 2023

Reviewer comment: An information request (IR) was sent to the Sponsor on December 2, 2020 requesting the following from the Sponsor:

- Consider the inclusion of MIS in both adults and children as an AESI since MIS can also occur in adults,*
- Consider modifications to the study design regarding recruitment and follow-up strategies to reduce the study burden on participants, since this study relies on self-enrollment and reporting by participants,*
- Provide narratives for two cases of Bell's palsy in the vaccine group, and any other cases of facial paralysis that occurred, and to add Bell's palsy as an AESI to all three active surveillance studies.*

In a response to the IR (EUA27034/0.12), the Sponsor agreed to add MIS in all ages and Bell's palsy as AESIs to their active surveillance studies. The Sponsor also provided strategies for ensuring recruitment goals are met and minimizing missing data. Some of these strategies include the use study site navigators and contractor platforms to assist with enrollment, and the use of a contractor call center for assistance with obtaining medical records and follow-up of study subjects who miss surveys. The Sponsor's responses are acceptable.

CBER identified additional comments and questions on this healthcare worker study. These include 1) specifying the list of AESIs to be evaluated in the study, 2) specifying the follow-up period for all outcomes, 3) adjusting study design and analytic parameters to make it an inferential study with the primary objective of evaluating the risk of specified AEs in the vaccinated population compared to a comparator time window or cohort instead of having a descriptive analysis as the primary objective, 4) not relying on the HERO registry as one of the main recruitment sources for the study, 5) modifying the study design in order to actively recruit participants and actively collect their data as opposed to the current plan which implements a passive recruitment and data collection strategy, 6) conducting the analysis per vaccine dose and overall, 7) verifying outcomes by medical chart review. These comments will be conveyed to the Sponsor to address when they submit their final study protocol.

5.1.2 Safety Surveillance of the Pfizer COVID-19 Vaccine in the U.S. Department of Defense Population Following Emergency Use Authorization (Protocol Number C4591011)

This study is an active safety surveillance evaluation among vaccine-exposed persons within the Department of Defense (DoD) Health System Databases using data derived from electronic health records (EHRs) and medical service claims among covered U.S. military and their families. The study objectives are:

Primary Objectives

- Estimate the real-world incidence of safety events of interest such as vaccine enhanced disease, which is potentially indicated by unexpected patterns of serious COVID-19-like illness among individuals vaccinated with the Pfizer-**

BioNTech COVID-19 vaccine, beginning with an EUA in a cohort of patients within the Department of Defense;

- Characterize the utilization patterns of vaccine recipients including estimating the proportion of participants in the Department of Defense healthcare system receiving vaccine, the completion and timing of the dosing schedule, and the demographics and health histories of recipients.

Secondary Objectives

- Evaluate whether the vaccine recipients experience increased risk of AESI post-vaccination;
- Estimate the incidence rates of AESI among subcohorts of interest such as women of childbearing age, immunocompromised people, and stratifications by age;
- Characterize utilization patterns of vaccine in subcohorts of interest such as women of childbearing age, immunocompromised, and within different age categories.

Subjects will include a cohort of all vaccine-exposed subjects and an unexposed comparison group in the DoD system. All subjects will have ≥ 6 months of enrollment in the healthcare system prior to vaccination in order to assess the subjects' baseline covariates. Outcomes of interest include: COVID-19-related hospitalization, respiratory failure, intensive care unit (ICU) admission, death, VAERD, clinically significant coagulation disorders, embolic events, and cardiac injury, multisystem inflammatory syndrome, serious immune-mediated conditions, and outcomes due to non-COVID 19 reasons: hospitalization, ICU admission, or death. The Sponsor plans to conduct comparative cohort analyses among patient subgroups using propensity score methods, and a self-controlled case series within the vaccine exposed cohort. The study will be conducted for 30 months.

The proposed milestones are:

- Final protocol submission: January 31, 2021
- Study completion date: June 30, 2023
- Final report submission: December 31, 2023

Reviewer comment: An information request was sent to the Sponsor on December 2, 2020 regarding whether Pfizer has an agreement with DoD. In a response to the information request (EUA27034/0.12), the Sponsor replied that they are in the process of securing agreements to access these data.

CBER identified additional comments and questions on this study in the DoD population. These include questions on 1) anticipated vaccine distribution and eligibility within this population, 2) how the study will capture records for health services provided outside of the military health service, 3) define analytic parameters for the self-controlled study design, 4) a list of AEs that will be evaluated in the study, 5) whether chart review will be performed to verify outcomes, 6) to modify study objectives and move the

secondary objective ‘to evaluate association between vaccine and AEs’ so it becomes a primary objective, 7) modify the cohort study design to become one of two primary study designs instead of a sensitivity analysis, and 8) define the follow-up period for the study. These comments will be conveyed to the Sponsor to address when they submit their final study protocol.

5.1.3 Post-Emergency Use Authorization Active Surveillance of Adverse Events of Special Interest among Individuals in the Veteran’s Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine (Protocol Number C4591012)

This study is an active surveillance study for AESIs and other clinically significant events associated with the Pfizer-BioNTech COVID-19 vaccine using the Veteran’s Health Administration (VHA) electronic medical record database. The study objectives are:

Primary Objectives

- Estimate the real-world incidence of safety events of interest such as vaccine enhanced disease, which is potentially indicated by unexpected patterns of serious COVID-19 illness, and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine beginning with an EUA in a cohort of patients within the US VHA;
- Characterize the utilization patterns of vaccine recipients among patients within VHA including estimating the proportion of patients receiving vaccine, the completion and timing of the dosing schedule, and the demographics and health histories of recipients.

Secondary Objectives

- Evaluate whether the vaccine recipients experience increased risk of AESI and other clinically significant events post-vaccination;
- Estimate the incidence rates of AESI and other clinically significant events among sub-populations of interest such as women of childbearing age, immunocompromised people, and stratifications by age;
- Characterize utilization patterns of vaccine in sub-populations of interest such as women of childbearing age, immunocompromised, and within different age categories.

The self-controlled risk interval design will be used to compare the risk interval following vaccination to non-risk intervals in the same individual. A historically-controlled cohort design will be used to monitor the occurrence of rare AESIs by comparing event frequencies in subjects who receive the Pfizer-BioNTech COVID-19 vaccine to event frequency among recipients of the seasonal influenza vaccine in five prior seasons. The study will be conducted for a period of 30 months following EUA issuance.

The proposed milestones are:

- Final protocol submission: January 31, 2021

- Study completion date: June 30, 2023
- Final report submission: December 31, 2023

Reviewer comment: An information request was sent to the Sponsor on December 2, 2020 regarding whether Pfizer has an agreement with the VHA. In a response to the information request dated December 4, 2020 (EUA27034/0.12), the Sponsor replied that they are in the process of securing agreements to access these data.

Questions identified by CBER include: 1) the specific list of AEs to be evaluated in the study need to be specified; 2) how the study plans to deal with incomplete healthcare data in the study population as many veterans receive some of their care outside the VHA system; 3) justification of the historical comparator of seasonal influenza vaccine; 4) analytic study parameters; 5) the self-controlled and cohort study designs are presented in a mixed form as a one-off study vs. sequential monitoring, and this needs to be clarified and justified; and 6) the inferential study objective which will evaluate the association between the vaccine and AEs needs to be moved to a primary study objective. These comments will be conveyed to the Sponsor to address when they submit their final study protocol.

6 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

6.1 Important Identified Risks

The Sponsor did not identify any important identified risks at this time.

6.2 Important Potential Risks

6.2.1 Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Disease enhancement due to vaccination against SARS-CoV-2 is a theoretical risk because VAED has been seen with other respiratory viruses and in animal models for coronavirus (8, 9). The possible mechanisms for VAED/VAERD include dysregulated T-cell responses that are skewed towards a T-helper type 2 response, antibody-mediated responses such as immune complexes or antibody-mediated enhanced disease, or dysregulated cytokine responses (10).

VAED is the worsened manifestations of infection in subjects infected with a wild-type pathogen who have previously been vaccinated against that pathogen. VAERD presentations primarily involve the lower respiratory tract. VAED/VAERD is expected to manifest as a worsened clinical presentation of SARS-CoV-2 viral infection in vaccinated subjects than would be expected given risk factors such as age and comorbidities (10). For example, subjects with a lower risk of severe COVID-19 could develop more severe disease, or patients with a higher risk for severe COVID-19 disease, such as older subjects or those with multiple medical comorbidities, could have an increased rate of fatal outcomes. In Study C4591001, there were 10 subjects who experienced severe COVID-19 disease, 9 of which were in the placebo group. The

Sponsor concludes these data suggest that the potential risk of VAED/VAERD is low at this time.

To further characterize the potential risk of VAED/VAERD, the Sponsor proposes completion of the Phase 1/2/3 randomized, placebo-controlled, observer-blind study of the safety, tolerability, immunogenicity, and efficacy of the product against COVID-19 in healthy subjects (Study C4591001). This study plans to conduct surveillance for two years after the second dose. The Sponsor considers an excess of COVID-19 disease and severe presentations as being possibly indicative for VAED/VAERD in the vaccinated population compared to the control group.

In addition to completion of studies under the IND, the Sponsor will perform active surveillance studies and AE reporting required under EUA. Vaccination providers will be instructed that reporting cases of COVID-19 that result in hospitalization or death is mandatory. The Sponsor has developed a data capture aid to assist with structured data collection from potential cases of VAED/VAERD in subjects with COVID-19 disease after vaccination. The Sponsor also proposes three post-authorization safety studies that include primary and secondary data collection for long-term active surveillance for safety events of interest, including severe or atypical COVID-19 disease among vaccinated subjects.

Reviewer comment: It will be difficult to separate manifestations VAED/VAERD from vaccine failure at the individual case level because the clinical symptoms of VAED/VAERD overlap that of natural disease. There are only 10 cases of severe COVID-19 (one in the vaccine group and nine in the placebo) in the Sponsor's safety database at the time of this review. Additionally, there is no long-term follow-up in most subjects currently. Thus, placebo-controlled studies with long-term follow-up are essential for examining an imbalance of severe COVID-19 disease manifestations in vaccinated subjects. The Sponsor's plan for evaluating the risk of VAED/VAERD is acceptable.

Multisystem Inflammatory Syndrome (MIS) is a syndrome associated with SARS-CoV-2 characterized by cardiac dysfunction, shock, and elevated markers of inflammation that occurs in both children and adults (11). As this syndrome may be immune-mediated, FDA suggested that MIS may be a theoretical risk that should be added as an Important Potential Risk to the Sponsor's PVP. In the response to an information request received November 30, 2020 (EUA27034/0.6), the Sponsor proposes not to add MIS as a standalone potential risk of safety concerns in the PVP. The Sponsor notes that cases of MIS have not been seen in the vaccinated participants of the Phase 1/2/3 clinical study. The Sponsor also states that surveillance for MIS and other systemic events will be evaluated in individual AE reports and aggregate report reviews, as well as in the active surveillance studies. The Sponsor proposes to add additional fields to capture MIS in their data capture aid. The Sponsor's response and proposed actions to monitor for MIS are acceptable.

At the time of submission, the PVP did not list anaphylactic reactions as a potential risk. However, in the UK three recipients of the Pfizer-BioNTech COVID-19 vaccine experienced hypersensitivity-related adverse events following vaccination. Per information received from the UK health authorities in an internal communication, one individual required treatment with IM epinephrine, and one with nebulized epinephrine. The third individual had what was described as mild allergic reaction and was treated with an anti-histamine. The individuals with the more severe symptoms had a previous history of allergies. The patient with the mild allergic reaction had no history of allergies. It was estimated that 15,000 individuals received the vaccine in the UK at the time of these adverse events. Anaphylaxis is a rare AE, with a reported lifetime incidence ranging from 20 to 42 cases per 100,000 person-years (12, 13). The Sponsor was requested to add anaphylactic reactions (including anaphylaxis) as an important potential risk to the PVP in an IR sent December 9, 2020. In a response to an IR received December 11, 2020 (EUA27034/0.24), the sponsor declined to add anaphylaxis to the PVP because the sponsor did not observe an imbalance of allergic or hypersensitivity reactions in the clinical studies and the labeling instructs use in an appropriate setting with properly trained personnel. The sponsor was notified that DE continues to recommend anaphylaxis be added to the PVP as the number of cases of anaphylactic reactions may be greater than expected, and will await additional safety analysis on this risk as more data is obtained from ongoing clinical trials and post-authorization use (IR sent December 11, 2020).

6.3 Important Missing Information

6.3.1 Use in Pregnancy and Lactation

Pregnant and lactating women were excluded from the clinical studies. The Sponsor proposes to perform a clinical study of the safety and immunogenicity of the product in pregnant women, with a protocol submission planned for February 2021. Active surveillance studies are also planned to monitor pregnancies exposed to the product under EUA; data describing the use, time of exposure, and adverse pregnancy outcomes will be described for such individuals identified within the studies, as feasible. The Sponsor also proposes to communicate this lack of data in the product labeling.

Reviewer comment: *The Sponsor's plan to address this missing information through additional studies in pregnant women and noting the lack of information in this population in the product labeling is acceptable.*

6.3.2 Vaccine Effectiveness

Vaccine efficacy was assessed during the pivotal clinical study. However, real-world vaccine effectiveness when the product is used in the general population with more diverse subjects is unknown. The Sponsor proposes to conduct a non-interventional study of individuals presenting with possible COVID-19 illness in a real-world setting to assess real-world effectiveness in comparison to clinical study efficacy results (protocol submission in Q1 2021). Immunogenicity studies are also planned in immunocompromised subjects to evaluate antibody and cell-mediated responses to

determine whether the product can induce potentially protective immune responses in this vulnerable population. The Sponsor also proposes to communicate efficacy data from the clinical study in the product labeling.

Reviewer comment: The Sponsor's proposal to collect additional information on vaccine effectiveness in the active surveillance studies is acceptable. Additional information on vaccine efficacy will come from completion of the pivotal study C4591001.

6.3.3 Use in Pediatric Individuals <16 years of Age

Pediatric subjects younger than 12 years of age were excluded from the pivotal clinical studies. Limited data for pediatric subjects between 12 and <16 years of age are available from recent inclusion in the Phase 3 study C4591001. The Sponsor plans two additional clinical studies of safety, efficacy, and immunogenicity in subjects under the age of 12. The Sponsor also plans to note that limited data are available from pediatric subjects in the product labeling.

Reviewer comment: The indications for use do not include pediatric subjects at this time. Thus, FDA requested the Sponsor include pediatric subjects under age 16 as an area of important missing information. The Sponsor's plan to perform additional studies in pediatric subjects and note the limited data in the product labeling is acceptable.

7 DE ASSESSMENT

The sponsor did not agree to an FDA request to add anaphylactic reactions (including anaphylaxis) to the PVP as an important potential risk. FDA continues to recommend anaphylaxis be added to the PVP given the recent post-market reports of anaphylactic reactions in vaccinated subjects in the U.K. The Sponsor's safety specifications otherwise adequately address the safety concerns identified from the clinical studies. At this time, Bell's palsy and appendicitis are not considered identified or potential risks in the PVP, and FDA will continue monitoring for Bell's palsy and appendicitis during the post-authorization period. Continuation of the Phase 3 pivotal study is essential for further characterization of the Important Potential Risk of VAED/VAERD after vaccination as well as the long-term assessment of safety and vaccine efficacy. Surveillance activities will include Sponsor pharmacovigilance processes with a data capture aid to evaluate cases of COVID-19 after vaccination for VAED/VAERD. The *Fact Sheet for Vaccination Providers* instructs healthcare providers of the mandatory reporting to VAERS of cases of COVID-19 resulting in death or hospitalization, MIS, SAEs, and medication errors. The Sponsor will conduct three active surveillance studies to characterize adverse events after vaccination, including direct surveying of vaccinated healthcare workers and two studies of claims/EHR data using the DoD and VHA databases. The Sponsor's plan for active surveillance and pharmacovigilance activities under EUA is acceptable.

8 DE RECOMMENDATIONS

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

compared to unvaccinated comparators. The study will be conducted for 30 months.

- Study Protocol Number C4591012. This study is an active surveillance study for adverse events of special interest and other clinically significant events associated with the Pfizer-BioNTech COVID-19 vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated subjects will be compared to unvaccinated subjects or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

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

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

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APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, Pharmacovigilance Plan
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, Lack of Effect and Disease Severity Data Capture Aid
November 20, 2020	Sponsor	EUA27034	Module 1.19, EUA
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, Safety Surveillance Plan
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, C4591008 Draft Protocol
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, C4591011 Draft Protocol
November 20, 2020	Sponsor	EUA27034	Module 1.16.1, C4591012 Draft Protocol
November 20, 2020	Sponsor	EUA27034	Module 1.14.1.3, Fact sheet for Health Care Providers
November 20, 2020	Sponsor	EUA27034	Module 1.14.1.3, Draft Labeling Text
November 20, 2020	Sponsor	EUA27034/0.1	Module 5.3.5.1, C4591001 Narratives
November 30, 2020	Sponsor	EUA27034/0.6	Module 1.11.3, Clinical Information Amendment, Response to CBER Regarding the Proposed Pharmacovigilance Plan
December 4, 2020	Sponsor	EUA27034/0.12	Module 1.11.3, Clinical Information Amendment, Response to CBER Regarding Reported Pregnancies, Response to CBER Regarding Cases of Bell's Palsy and Active Surveillance Studies
December 7, 2020	Sponsor	EUA27034/0.15	Module 1.16, Revised Pharmacovigilance Plan and Data Capture Aid
December 9, 2020	Sponsor	EUA27034/0.20	Module 1.19, Revised EUA Document
December 9, 2020	Sponsor	EUA27034/0.22	Module 1.11.3, Clinical Information Amendment, Response to CBER Regarding Milestones for Active Surveillance Studies
December 11, 2020	Sponsor	EUA27034/0.24	Module 1.11.3, Clinical Information Amendment, Response to Pharmacovigilance IR