



**BNT162b2 (COMIRNATY)**

**BLA STN 125742/0**

**Response to CBER 13 August 2021 Information Request Regarding  
Safety-Related Postmarketing Requirement/Postmarketing Commitment Studies**

**16 August 2021**

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**TABLE OF CONTENTS**

1. INTRODUCTION .....3

2. CBER REQUESTS AND SPONSOR RESPONSES .....3

    2.1. CBER Request 1 - Postmarketing Requirements .....3

    2.2. CBER Request 2 – Postmarketing Commitments .....6

    2.3. CBER Request 3 – Study Milestones .....8

    2.4. CBER Request 4.....11

    2.5. CBER Request 5.....11

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## 1. INTRODUCTION

Reference is made to BLA STN 125742/0 for COVID-19 mRNA Vaccine (COMIRNATY), for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals  $\geq 16$  years of age and to CBER's Information Request received via email on 13 August 2021.

CBER requests are presented in *bold italics* followed by Pfizer-BioNTech response in plain text.

## 2. CBER REQUESTS AND SPONSOR RESPONSES

*Our review of your pharmacovigilance plan for COMIRNATY (COVID-19 Vaccine, mRNA) under BLA STN 125742/0 is ongoing.*

*Should this product be approved, we have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) will not be sufficient to identify:*

- *known serious risks of myocarditis and pericarditis*
- *an unexpected serious risk of subclinical myocarditis*

### 2.1. CBER Request 1 - Postmarketing Requirements

*Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks. Therefore, should this product be approved, we have determined that you will be required to conduct the following studies as postmarketing requirements (PMRs) under Section 505(o) of FDCA:*

1. *Epidemiologic studies using large electronic healthcare databases to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY*
  - a. *US – Sentinel system (C4591009)*
  - b. *EU active surveillance study (C4591021)*
  - c. *EU active surveillance substudy (C4591021)*

### Sponsor Response

Pfizer/BioNTech acknowledges CBER's request and will conduct the following studies as postmarketing requirements (PMRs) under Section 505(o) of FDCA:

- a. Study C4591009 entitled, "A Non-interventional Post Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States" is a planned PMR to assess the occurrence of safety events of interest in the general US population of all ages, pregnant women, the immunocompromised and persons with a prior history of

COVID-19 within selected data sources participating in the US Sentinel System. Individuals receiving the vaccine since receipt of EUA on 11 December 2020 will be captured. Protocol submission is planned for 31 August 2021. A monitoring report will be submitted by 31 October 2022; an interim report by 31 October 2023; and a final study report by 31 October 2025.

- b. Study C4591021, Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine, conducted in collaboration with the VAC4EU Consortium Team, is a commitment made to EMA. The final protocol was approved by the European Medicines Agency on 24 June 2021. The final protocol was submitted to CBER on 11 August 2021 as part of the Response to 10 August 2021 Information Request Regarding Post-Marketing Safety Studies.
  - c. A substudy of C4591021 is planned to describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status (medical record review), risk factors, and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine. A synopsis of the study was provided as part of the Response to CBER 10 August 2021 Information Request Regarding Post-Marketing Safety Studies, which was submitted on 11 August 2021. This substudy is still under development and subject to change based on data availability and feedback from EMA. Pfizer/BioNTech will share the final protocol with FDA following EMA endorsement.
2. *A prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network)*

### **Sponsor Response**

This study will enroll patients <21 years of age who are diagnosed with vaccine-associated myocarditis within the Pediatric Heart Network (PHN) during the study period and who fulfill study inclusion criteria (yet to be determined, will include informed consent). A full IRB and DSMB approved protocol will be shared with the agency by 30 November 2021 and will include sample size estimates. The estimation of study size in the study protocol will require assumptions about future approvals of vaccines, numbers of people vaccinated by age, gender, type of vaccine and dose, effects of each vaccine by dose, number of participating PHN sites, etc. These scenarios will be elaborated in a study protocol under preparation with our PHN collaborators. Pfizer/BioNTech will plan for a 5-year follow-up period. Feasibility discussions with our PHN collaborators are ongoing; should any issues or unexpected challenges emerge, Pfizer/BioNTech will inform the agency promptly.

**3. *A prospective study to assess the incidence of subclinical myocarditis following vaccination***

***Regarding the study to further characterize subclinical myocarditis, we acknowledge that you are in the process of analyzing Troponin I levels in serum samples to determine the background rate of abnormality of this biomarker in the relevant population. We acknowledge the challenge in projecting a definitive sample size or dates for a future study to assess the incidence of subclinical myocarditis. However, we request that you propose your plans for a future prospective study to assess the incidence of subclinical myocarditis, including projected study milestone dates.***

**Sponsor Response**

Reference is made to our most recent correspondence with the Agency on this topic, as described in Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies submitted to BLA on 11 August 2021.

As noted, we proposed to analyze troponin I levels at a central laboratory in samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in the C4591001 study, prior to receipt of BNT162b2 (ie, either at baseline, or at any visit for placebo recipients prior to cross-over). This is planned to include 3000 samples, stratified equally in the 12-17-, 18-24-, and 25-30-years age groups.

The current status of this work is as follows. A central laboratory that can perform the work has been identified; contracting and logistical aspects are being prepared: 3000 appropriate samples have been identified, retrieved from frozen storage, aliquoted and shipped to the central laboratory. The samples then need to be tested and the data analyzed and interpreted. This work is anticipated to be completed by the end of December 2021.

Furthermore, in a response to the Agency's recommendation to collect and store blood samples during the time period when symptomatic myocarditis cases have most frequently been reported (ie, within the first 4 days post-vaccination), submitted to BB-IND 17936 on 04 August 2021 (SN 0436), we made the following proposal but have not received feedback on this proposal at this time.

We proposed to schedule a blood draw to obtain a serum sample for storage and potential future troponin testing, at baseline and 2-5 days after the second or third dose of BNT162b2 in two studies.

**C4591007:** Pfizer/BioNTech proposed to add 750 participants 5 to <12 years of age (randomized 2:1 to receive BNT162b2 10 µg or placebo) and 500 participants 12-15 years of age (open label receipt of BNT162b2 30 µg). These participants would be introduced through a protocol amendment.

**C4591031:** Pfizer/BioNTech proposed to add a new substudy of 1000 participants with documented receipt of 2 prior 30 µg doses of BNT162b2 (the second dose received at least

6 months ago), 16 to 30 years of age (randomized 1:1 in a crossover design to receive 30 µg BNT162b2 or placebo at baseline and the alternative 4 weeks later).

We reiterate our caution, which the Agency has acknowledged, that there is no widely accepted definition of subclinical myocarditis. Neither ECG abnormalities, nor elevated troponin levels, are specific to symptomatic myocarditis, and certainly not to subclinical myocarditis. Therefore, there remain many unknowns with respect to the feasibility and design of any potential prospective study of subclinical myocarditis. In light of that, our current proposal for a prospective study to assess the incidence of subclinical myocarditis following vaccination in individuals  $\geq 16$  years:

- Analysis of baseline troponin I test results will be available by the end of December 2021.
- During this same period of time we will prepare to start enrollment of 1000 participants into the C4591031 substudy in January 2022.
- Assuming that subclinical myocarditis can be defined on the basis of elevated troponin I, and that the baseline analysis indicates that such a study is feasible, we will consider C4591031 to be the prospective study to assess the incidence of subclinical myocarditis following vaccination in individuals  $\geq 16$  years. If the sample size of 1000 is insufficient, it will be increased through a protocol amendment.
- Projected study milestone dates (if sample size were to be increased to 3000) would be as follows:
  - Final protocol submission: 30 November 2021;
  - Study completion: 30 June 2022;
  - Interim reports: not applicable;
  - Final study report: 31 December 2022.

## 2.2. CBER Request 2 – Postmarketing Commitments

*Additionally, should this product be approved, your proposed studies listed below will be postmarketing commitments (PMCs) as agreed upon between FDA and the applicant:*

1. *A pregnancy registry for COMIRNATY to assess pregnancy and infant outcomes after exposure of COMIRNATY during pregnancy in the Organization of Teratology Information Specialists (OTIS)/Mother to Baby Pregnancy Registry (C4591022)*

### Sponsor Response

Pfizer/BioNTech acknowledges CBER's request and will conduct Study 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,” as a PMC.

This prospective, observational cohort study will assess pregnancy and infant outcomes after exposure to COMIRNATY during pregnancy among pregnant women aged 18 years or older who reside in the US or Canada. Pregnant women who participate in the OTIS Pregnancy Registry and receive the vaccine on or after 11 December 2020 (ie, date FDA granted EUA for the Pfizer-BioNTech COVID-19 vaccine) will be captured. The protocol was submitted on 01 July 2021. Annual interim reports will be submitted on 31 January 2022, 31 January 2023, 31 January 2024, and 31 January 2025. A final study report will be submitted by 01 December 2025.

- 2. A placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of BNT162b2 in healthy pregnant women  $\geq 18$  years of age (C4591015)***

***For study C4591015, please comment on recruitment and retention of study participants to date, including any barriers that you have encountered. Please comment on the feasibility of completing the trial, as planned, considering CDC’s recommendation of COVID-19 vaccination for all people 12 years and older, including people who are pregnant ([https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html#anchor\\_1628692562866](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html#anchor_1628692562866)).***

### **Sponsor Response**

C4591015 is a global Phase 2/3, randomized, placebo-controlled, observer-blind study evaluating the safety, tolerability, and immunogenicity of 30  $\mu\text{g}$  of BNT162b2 or placebo administered in 2 doses, 21 days apart, in approximately 700 healthy pregnant women 18 years of age or older vaccinated at 24 to 34 weeks’ gestation. Participants are being randomized 1:1 to receive BNT162b2 or placebo (saline). Participating countries are US, Spain, UK, South Africa, Brazil and Mozambique. All countries are active, with the exception of Mozambique where enrollment is due to start in October 2021.

Enrollment has been challenging due to recommendations for immunization of pregnant women in all participating countries, except Mozambique, where such a recommendation is anticipated shortly. As of 13 August 2021, enrollment was 259 out of the planned 700. Anticipated enrollment by December is approximately 450 participants. Retention does not appear problematic once participants are enrolled, with approximately 6% withdrawn from the study due to request by participant, almost all participants in Phase 2 having received a second dose and 124 having already delivered their infants.

An Internal Review Committee met on 05 August 2021 to review the Phase 2 reactogenicity and safety data through 7 days after the second dose, and recommended that the study continue.

There is concern that the study may have trouble reaching the full enrollment. At present the intention is to complete the study if at all possible, because of the importance of a placebo-controlled safety assessment in pregnancy.

**3. *An active safety surveillance study among individuals in the Veteran’s Affairs Health System (C4591012)***

**Sponsor Response**

Study 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” is an ongoing active surveillance PMC to assess whether individuals in the US Veteran’s Affairs Health System overall and in subcohorts of interest experience an increased risk of safety events of interest, following receipt of the Pfizer-BioNTech COVID-19 Vaccine. The study period will be approximately 30 months following availability of vaccine under EUA. A study protocol was submitted to FDA on 29 January 2021. A protocol amendment to address analyses requested by CBER on 12 May and 10 August 2021 will be submitted to the FDA by 31 August 2021. A first interim report was submitted to BB-IND 19736 (SN 0386) and EUA 27034 on 30 June 2021. Additional interim reports are planned for 31 December 2021, 30 June 2022 and 31 December 2022. A final study report will be submitted by 31 December 2023.

**4. *Study C4591014, Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California***

***For Study C4591014, please comment on the feasibility of revising or amending the protocol to also collect information on the incidence of myocarditis and pericarditis and to include individuals 12 through 15 years of age.***

**Sponsor Response**

Study C4591014 will be amended to include individuals 12 through 15 years of age in vaccine effectiveness calculations. Safety endpoints, however, will not be collected in this study and are better-suited to be collected in other ongoing post-authorization safety studies.

**2.3. CBER Request 3 – Study Milestones**

***Please confirm the study milestone dates (mm/dd/yyyy) in the tables below, and populate the projected study milestone dates for PMR#3 (subclinical myocarditis) as per the above request.***

***Note that we have also included dates for interim reports when applicable.***

**Sponsor Response**

Study milestones have been updated (in **bold** font) in the below tables.

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<b>Milestone dates</b>	<b>PMR #1a: C4591009 (Sentinel)</b>	<b>PMR #1b: C4591021 (EU)</b>	<b>PMR #1c: C4591021 substudy (EU)</b>	<b>PMR#2: PHN registry</b>	<b>PMR#3: subclinical myocarditis</b>
Final protocol submission	08/31/2021	08/11/2021	<b>Subsequent to EMA approval, estimated 01/31/2022</b>	11/30/2021	<b>11/30/2021</b>
Study completion	06/30/2025	09/30/2024	09/30/2024	12/01/2026	<b>06/30/22</b>
Interim reports	Monitoring report: 10/31/2022 Interim report: 10/31/2023	Progress report: 09/30/2021 Interim report 1: 03/31/2022 Interim report 2: 09/30/2022 Interim report 3: 03/31/2023 Interim report 4: 09/30/2023 Interim report 5: 03/31/2024			<b>Not applicable</b>
Final study report	10/31/2025	09/30/2024	09/30/2024	<b>05/01/2027</b>	<b>12/31/2022</b>

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<b>Milestone dates</b>	PMC #1: C4591022 pregnancy registry	PMC#2: C4591015 RCT pregnant women	PMC#3: C4591012 VA study	PMC #4: C4591014 Kaiser study
Final protocol submission	07/01/2021	12/22/2020	1/29/2021	3/22/2021
Study completion	<b>06/01/2025</b>	10/31/2022	06/10/2023	
Interim reports	<b>Interim report 1: 01/31/2022 Interim report 2: 01/31/2023 Interim report 3: 01/31/2024 Interim report 4: 01/31/2025</b>		Interim report 1: 06/30/2021 Interim report 2: 12/31/2021 Interim report 3: 06/30/2022 Interim report 4: 12/31/2022	
Final study report	12/01/2025	5/31/2023	12/31/2023	<b>06/30/2023</b>

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## 2.4. CBER Request 4

*Please also propose study(ies) in adolescents 12 through 17 years of age to evaluate the safety and immunogenicity of lower doses of COMIRNATY.*

### **Sponsor Response**

Pfizer/BioNTech submitted protocol amendment 2 to BB-IND 19736 for Study C4591007 to the Agency on 10 August 2021 (SN 0443).

This protocol amendment includes Phase 1 evaluation of dose levels of 3 µg and 10 µg in individuals 12 to <16 years of age and 16 to <30 years of age (32 participants per dose level and age group). Based on the results from Phase 1, one dose level will be selected for each age group for Phase 3 evaluation of safety and immunogenicity in 300 participants per age group.

## 2.5. CBER Request 5

### **Voluntary sponsor studies**

*For the following voluntary sponsor studies, please provide study status updates in your periodic safety reports:*

- *C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization*
- *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*

### **Sponsor Response**

Pfizer/BioNTech will provide study status updates regarding Study C4591011 and Study C4591008 in periodic safety reports.

## Document Approval Record

<b>Document Name:</b>	COVID-19 Vaccine Response to FDA IR 13-Aug-2021 - PMR_PMC Studies
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