From: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>
Sent: Friday, August 13, 2021 7:12 PM
To: Harkins Tull, Elisa <Elisa.HarkinsTull@pfizer.com>
Cc: Smith, Michael (CBER) <Michael.Smith2@fda.hhs.gov>; Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>; Aghajani Memar, Neda <Neda.AghajaniMemar@pfizer.com>; Devlin, Carmel M <Carmel.Devlin@pfizer.com>
Subject: STN 125742/0 – COMIRNATY (COVID-19 Vaccine, mRNA) - Safety-related Postmarketing Requirement/Postmarketing Commitment studies

Dear Ms. Harkins,

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

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)

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)

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.

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)

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

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

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.

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).

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.

Milestone dates	PMR #1a: C4591009 (Sentinel)	PMR #1b: C4591021 (EU)	PMR #1c: C4591021 substudy (EU)	PMR#2: PHN registry	PMR#3: subclinical myocarditis
Final protocol submission	8/31/2021	8/11/2021	12/31/2021	11/30/2021	
Study completion	06/30/2025	9/30/2024	9/30/2024	12/01/2026	
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			

Final study report	10/31/2025	9/30/2024	09/30/2024	10/31/2025	

Milestone dates	PMC #1: C4591022 pregnancy registry	PMC#2: C4591015 RCT pregnant women	PMC#3: C4591012 VA study	PMC #4: C4591014 Kaiser study
Final protocol submission	7/1/2021	12/22/2020	1/29/2021	3/22/2021
Study completion	08/01/2025	10/31/2022	06/10/2023	
Interim reports			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	12/1/2025	5/31/2023	12/31/2023	

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

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

Please provide your responses in an amendment to STN 125742/0 by COB Monday, August 16, 2021. We recommend that you restate each item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference.

Please confirm receipt of this email and let me know if you have any questions or need additional information.

Regards,

Ram

Ramachandra S. Naik, Ph.D.
Biologist (Regulatory) / Primary Reviewer
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review

U.S. Food and Drug Administration
Tel: 301-796-2640
ramachandra.naik@fda.hhs.gov