From: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>
Sent: Tuesday, August 10, 2021 12:01 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: BLA 125742/0 – COMIRNATY (COVID-19 Vaccine, mRNA) - Comments regarding safety-related postmarketing studies

Dear Ms. Harkins,

Our review of your pharmacovigilance plan for COMIRNATY (COVID-19 Vaccine, mRNA) under BLA 125742 is ongoing. We are reviewing your response (submitted in amendment 30 dated August 3, 2021) to our July 28, 2021 information request regarding postmarketing safety studies, and have the following comments:

1. The primary analysis in the post-authorization safety study C4591009 protocol synopsis uses a concurrent unexposed cohort. People without vaccination codes could receive their COVID vaccinations outside of the system, and exposure misclassification could bias the results. The self-controlled methods such as self-controlled risk interval (SCRI) are less susceptible to bias due to exposure misclassification. SCRI with a post-vaccination control window was proposed as a sensitivity analysis.

   Please clarify how you plan to assess the magnitude of exposure misclassification for the concurrent unexposed cohort and quantify the bias. If the magnitude of the exposure misclassification is large, please consider using the SCRI as the primary analysis. The proposed SCRI control window has the same length as the risk interval, which may decrease the risk of time-varying confounding bias but could result in more limited person time for some AESIs thus impacting the power of the SCRI analysis. Since SCRI allows the control window to have a different length than the risk window, please consider using a longer control window (e.g., multiples of the risk window) in the primary analysis, while maintaining the shorter control window for a sensitivity analysis. Please provide length of risk interval for each AESI.

2. Table 1 on Page 5 of the Response to Information Request provided the required number of cases to detect myocarditis under different assumptions with a self-controlled case series (SCCS) analysis. The study C4591009 protocol synopsis proposed a SCRI analysis. SCCS samples cases only, SCRI samples vaccinated individuals only, and the control interval could differ between these two study designs even with the same length of risk interval. Please clarify the length and definition of control interval in the Table 1 sample size calculation. The choice of risk window is critical for SCRI. Because the onset of myocarditis was typically within several days after mRNA COVID-19 vaccination, please add a 7-day risk window to the SCRI analysis in addition to the proposed 14-day and 21-day risk window. Please also provide the sample size calculation for a 7-day risk window for myocarditis.

   For study C4591009 protocol synopsis, the sample size calculation on Page 14 was based on a true RR=1. Please recalculate the sample size under alternative RRs.

3. Please clarify when patient accrual will be completed for study C4591009.

4. Please provide the study completion date (in mm/dd/yyyy format) for the following studies:
   a. C4591009
   b. C4591022
   c. C4591012
   d. C4591015
   e. C4591021 and C4591021 substudy
   f. Registry study with Pediatric Heart Network (PHN)

5. For the registry study with PHN, you have stated that you have identified approximately 130 patients and plan to enroll additional patients. Please provide a proposed sample size for this study, and the basis for the sample size calculation. You have also proposed 1-year prospective follow-up. We request 5 years of follow-up to capture potential long-term sequelae of myocarditis after vaccination.

6. Please provide the protocol synopses and current status for the study C4591021 and C4591021 substudy.

7. You have proposed to analyze troponin I levels at a central laboratory in 3,000 samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in BNT162b2 studies, prior to receipt of BNT162b2. We acknowledge that the results of this analysis will help determine what sample size might be required for a prospective study to assess the incidence of subclinical myocarditis following vaccination. Please provide projected dates for the Final Protocol Submission, Study Completion, and Final Report Submission for a prospective study to assess the incidence of subclinical myocarditis following vaccination.

Please provide your responses in an amendment to STN 125742/0 by 2:00 PM on Wednesday, August 11, 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

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