

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

**PHARMACOVIGILANCE PLAN REVIEW: ADDENDUM MEMORANDUM**

From: Meghna Alimchandani, MD  
Deputy Director, Division of Epidemiology (DE)

Kerry Welsh, MD  
Medical Officer, Analytic Epidemiology Branch (AEB)

To: Ramachandra Naik, PhD  
Chair, Review Committee  
Office of Vaccines Research and Review (OVRR), CBER,  
FDA

Through: Manette Niu, MD  
Branch Chief, AEB  
DE, OBE, CBER, FDA

Narayan Nair, MD  
Division Director, DE  
OBE, CBER, FDA

Subject: Review of Pharmacovigilance Plan – Addendum memo

Sponsor: Pfizer

Product: COMIRNATY; BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)

BLA Number: 125742/0

Proposed Indication: Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals  $\geq 16$  years of age.

Submission Date: May 18, 2021

Action Due Date: January 16, 2022

## 1 Objectives and Scope

The sponsor's proposed pharmacovigilance plan (PVP), clinical safety database and post-authorization safety data were reviewed in the OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021 (OBE/DE primary reviewer: Deborah Thompson, MD). This addendum memo serves to provide review updates, including additional VAERS analysis for adverse events of special interest, and new information on sponsor proposed postmarketing safety studies, and final OBE/DE recommendations for postmarket safety monitoring for COMIRNATY.

## 2 Vaccine Adverse Event Reporting System Data

FDA post-authorization safety data was previously summarized in section 6 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021. A COVID-19 Vaccine Safety Update<sup>1</sup> from the European Medicines Agency (EMA) prompted further VAERS analysis of the following adverse events of special interest (AESI): erythema multiforme; glomerulonephritis and nephrotic syndrome; menstrual disorders.

- Erythema multiforme (EM), Stevens-Johnson Syndrome, and toxic epidermal necrolysis:

A query<sup>2</sup> of the VAERS database on August 16, 2021, retrieved 194 reports of which there were 53 U.S. reports. Among U.S. reports (n = 53), there were 12 serious reports including 1 death:

- The patient that died (VAERS ID 1034116) was a 58 year old female who presented with 3 - 4 days of extensive rash with skin sloughing 11 days after vaccination. Skin biopsy was compatible with toxic epidermal necrolysis. She died (b) (6) days after vaccination.

Cases involved 29 females, 23 males and sex was unknown in one case. Median age was 56 years (range 13 – 98 years, unknown for 5 cases). Interval to onset of symptoms post vaccination was 2 days (range 0 – 45 days, unknown for 3 cases).

- Glomerulonephritis and nephrotic syndrome:

A query<sup>3</sup> of the VAERS database on August 16, 2021, retrieved 175 reports of which there were 57 U.S. reports. Among U.S. reports (n = 57), there were 35 serious reports. There were no deaths. Cases involved 24 females, 32 males and sex was not reported in one case. Median age was 40 years (range 12 – 88

---

<sup>1</sup> [https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-11-august-2021\\_en.pdf](https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-spikevax-previously-covid-19-vaccine-moderna-11-august-2021_en.pdf)

<sup>2</sup> Preferred Terms (PTs) for query: ERYTHEMA MULTIFORME;STEVENS-JOHNSON SYNDROME;TOXIC EPIDERMAL NECROLYSIS

<sup>3</sup> PTs for query: ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE;C3 GLOMERULOPATHY;FIBRILLARY GLOMERULONEPHRITIS;FOCAL SEGMENTAL GLOMERULOSCLEROSIS;GLOMERULONEPHRITIS;GLOMERULONEPHRITIS ACUTE;GLOMERULONEPHRITIS CHRONIC;GLOMERULONEPHRITIS MEMBRANOPROLIFERATIVE;GLOMERULONEPHRITIS MEMBRANOUS;GLOMERULONEPHRITIS MINIMAL LESION;GLOMERULONEPHRITIS PROLIFERATIVE;GLOMERULONEPHRITIS RAPIDLY PROGRESSIVE;GOODPASTURES SYNDROME;GRANULOMATOSIS WITH POLYANGIITIS;HENOCH-SCHONLEIN PURPURA;HENOCH-SCHONLEIN PURPURA NEPHRITIS;IGA NEPHROPATHY;IGM NEPHROPATHY;MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS;MICROSCOPIC POLYANGIITIS;NEPHRITIC SYNDROME;NEPHRITIS ALLERGIC;NEPHRITIS;NEPHRITIS INTERSTITIAL;NEPHROTIC SYNDROME

years, unknown for 2 cases). Interval to onset of symptoms post vaccination was 2.5 days (range 0 – 48 days, unknown for 3 cases).

- **Menstrual disorders:**

A query<sup>4</sup> of the VAERS database on August 16, 2021, retrieved 7249 reports of which there were 3327 U.S. reports. Twenty-eight U.S. reports were excluded because sex was reported as male, or sex was not reported. Among U.S. cases in females only (n = 3299), there were 85 serious reports. There were no deaths. Median age was 37 years (range 12 – 74 years, unknown for 107 cases). Interval to onset of symptoms post vaccination was median 3 days (range 0 – 154 days, unknown for 158 cases).

*Reviewer comment:* Note that the above analysis is based on case counts retrieved from automated queries, and individual cases were not manually reviewed. Limitations of passive surveillance data include missing/incomplete data and unconfirmed diagnoses. In the context of 201,577,973 doses of Pfizer-BioNTech COVID-19 Vaccine administered<sup>5</sup>, there are no new safety signals identified from the above analysis of VAERS data at this time. Based on the above query results, there were few U.S. reports for erythema multiforme (n = 53 U.S.) and glomerulonephritis and nephrotic syndrome (n = 57 U.S. reports). Majority of the reports of menstrual disorders were non-serious reports. Menstrual disorders are common in the general population and can occur without an underlying medical condition. OBE/DE will continue safety monitoring for adverse events after COMIRNATY. We will review any additional information on these AESIs from EMA when available.

### **3 Serious risks: myocarditis and pericarditis, and subclinical myocarditis**

Myocarditis and pericarditis: Post-authorization safety data (previously described in section 6 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021) has identified serious risks for myocarditis and pericarditis after COMIRNATY, with increased risk in males under 30 years of age, particularly following the second dose, and onset of symptoms within 7 days following vaccination. Authorized EUA Fact Sheets were updated on June 25, 2021, to include a new Warning about myocarditis and pericarditis.

Subclinical myocarditis: Incidence of subclinical myocarditis and potential long-term sequelae following COMIRNATY are unknown. A previous study<sup>6</sup> of smallpox vaccine

---

<sup>4</sup> PTs for query: ABNORMAL UTERINE BLEEDING;ABNORMAL WITHDRAWAL BLEEDING;ANOVULATORY CYCLE;BLEEDING ANOVULATORY; DELAYED MENARCHE;DYSMENORRHOEA;INTERMENSTRUAL BLEEDING;MENSTRUAL DISORDER;MENSTRUAL DISCOMFORT; MENSTRUATION IRREGULAR;PREMENSTRUAL DYSPHORIC DISORDER;PREMENSTRUAL PAIN;PREMENSTRUAL SYNDROME;WITHDRAWAL BLEED; AMENORRHOEA; HYPOMENORRHOEA;MENSTRUATION DELAYED; OLIGOMENORRHOEA;HEAVY MENSTRUAL BLEEDING; MENOMETRORRHAGIA; POLYMENORRHAGIA; POLYMENORRHOEA

<sup>5</sup> CDC COVID Data Tracker accessed on August 18, 2021 [https://covid.cdc.gov/covid-data-tracker/#vaccinations\\_vacc-total-admin-rate-total](https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total)

<sup>6</sup> Engler RJ, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. PLoS One. 2015;10(3):e0118283

suggested an incidence of possible subclinical myocarditis (based on cardiac troponin T elevations) 60-times higher than the incidence rate of overt clinical myocarditis.

FDA information request dated July 28, 2021, asked the sponsor to propose postmarketing observational safety study(ies) to assess myocarditis and pericarditis following administration of COMIRNATY to quantify the magnitude of risk by age, sex, and dose; include follow up cases (e.g., via a registry) for recovery status and long-term sequelae; and propose plans to characterize subclinical cases of myocarditis. The sponsor's proposed plans were reviewed (responses to Information Requests dated July 28, 2021, and August 10, 2021) and recommendations for proposed safety postmarketing requirements/commitments (PMRs/PMCs) as well as CBER Sentinel Sufficiency assessment were presented to the CBER Safety Working Group (SWG) on August 12, 2021.

#### **4 Sponsor proposed post-authorization/postmarketing safety studies**

The safety surveillance studies proposed by the Sponsor were previously reviewed in section 7.3 of OBE/DE Pharmacovigilance Plan Review Memorandum, dated August 6, 2021. Additional information provided by the sponsor is summarized below.

##### Studies to assess risks of myocarditis, pericarditis and subclinical myocarditis

- C4591021 and C4591021 substudy (EU): *Post Conditional Approval Active Surveillance Study Among Individuals in Europe*
  - C4591021 is a retrospective cohort study and the C4591021 substudy is a natural history cohort study within a retrospective cohort study. The substudy plans to collect follow-up for treatment for myocarditis and pericarditis, clinical outcomes, and recovery. The data source comprises of electronic healthcare databases in Netherlands, Norway, United Kingdom, Italy and Spain. The sponsor estimates that the EU databases will capture approximately 4.1 million individuals  $\leq 30$  years of age with exposure to COMIRNATY. The final protocol for study C4591021 was approved by the EMA on June 24, 2021, and this protocol was submitted to FDA for review on August 11, 2021 and is currently under review.<sup>7</sup>
- Prospective cohort registry study for long term follow-up, in collaboration with Pediatric Heart Network (PHN). PHN is a multi-center consortium of hospitals across U.S. and Canada that conducts research for congenital and pediatric-acquired heart disease. The National Institutes of Health (NIH)/National Heart, Lung and Blood Institute (NHLBI) provides funding for PHN. The sponsor identified approximately 130 patients (as of August 2021), who presented to PHN

---

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0118283>

<sup>7</sup> Note that review of study protocols are documented in separate protocol review memorandums.

sites after receiving a COVID-19 vaccine and were diagnosed with myocarditis. The sponsor states that, “additional patients continue to present and could be enrolled.” Projected sample size and statistical analysis plan will be provided upon submission of the final study protocol on November 30, 2021. In accordance with FDA recommendations, the sponsor has agreed to follow subjects prospectively for 5 years. The objectives of the study include:

- Characterize the clinical course of acute post-vaccine myocarditis
- Characterize potential long-term sequelae and quality of life
- Compare long-term effects of post-vaccine myocarditis with those of nonvaccine myocarditis, including myocarditis arising in COVID-infected persons
- Identify possible risk factors for post-vaccine myocarditis (including age, sex, race, ethnicity, obesity, and other factors)
- Plans by Sponsor to characterize subclinical cases of myocarditis:
  - The sponsor has expressed challenges in proposing a potential prospective study of subclinical myocarditis because of the absence of a definition of subclinical myocarditis and unknown background incidence of troponin abnormalities. As an initial step, the sponsor plans to determine the background rate of abnormal troponin levels by analyzing troponin I levels in samples of stored sera (drawn <1 year ago) in 12-30-year-old individuals participating in BNT162b2 studies, prior to receipt of BNT162b2 (i.e., either at baseline, or at any visit for placebo recipients). Three thousand samples, stratified in the 12-17, 18-24 and 25-30 years age group, will be analyzed (there is a 95% probability of observing one abnormal result amongst the overall sample if the background rate of abnormality is 0.1%). The sponsor anticipates this analysis to be completed by the end of December 2021.
  - The sponsor has proposed modifications to the following two trials 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:
    - Study C4591007: proposed addition of 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).
    - C4591031 substudy: proposed addition of a new substudy of 1000 subjects 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).
  - As per the sponsor, “*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.”*

## **5 CBER Safety Working Group (SWG) concurrence with proposed safety postmarketing requirements/commitments (PMRs/PMCs)**

Based on review of available data, there are known risks for myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis, which warrant PMR safety studies to assess these serious risks. The CBER Sentinel Program was deemed to be insufficient to assess the serious risks of myocarditis and pericarditis, and subclinical myocarditis for the following reasons (please also see Sentinel Sufficiency memorandum):

- At the time of BLA approval, the data sources in the CBER Sentinel Program are not sufficient to identify the outcomes due to lack of sufficient power to assess the magnitude of risk in patients 12-30 years of age.
- In addition, CBER Sentinel Program is not sufficient to follow up cases for recovery status and long-term sequelae of myocarditis and pericarditis, or for identification and characterization of subclinical myocarditis cases.

Furthermore, the FDA and applicant have agreed upon safety studies as PMCs to (a) assess safety in pregnant women and, (b) an active surveillance study in the Veteran's Affair Health System database, which includes sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose Pfizer vaccine, and individuals with prior SARS-CoV-2 infection).

During a meeting on August 12, 2021, the CBER Safety Working Group concurred with the review team's proposed PMRs/PMCs:

- Postmarketing requirements (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA) to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis:
  1. Epidemiologic studies using large electronic healthcare databases to evaluate the occurrence of myocarditis and pericarditis
    - a) US – Sentinel system (C4591009)
    - b) EU – active surveillance study (C4591021 and C4591021 substudy)
  2. Registry for long-term follow-up (in collaboration with Pediatric Heart Network)
  3. Prospective study to assess the incidence of subclinical myocarditis following vaccination
- Postmarketing commitments (PMCs):

1. Pregnancy registry study to assess pregnancy and infant outcomes after exposure to COMIRNATY during pregnancy among pregnant women aged 18 years or older<sup>8</sup> who reside in the US or Canada. (C4591022)
2. Randomized controlled trial (RCT) in pregnant women (C4591015)
3. Active safety surveillance study among persons in the Veteran's Affairs Health System (C4591012)

The sponsor was notified of the above PMRs/PMCs in an Information Request (IR) dated August 13, 2021.

***Updates since August 12, 2021 SWG meeting:***

- During the SWG meeting, there were questions raised regarding the feasibility of completing the RCT in pregnant women (C4591015), as planned, considering CDC's recommendation<sup>9</sup> of COVID-19 vaccination for all people 12 years and older, including people who are pregnant. In further communication with the sponsor, Pfizer described this as a global study that included sites outside the U.S. The Sponsor acknowledged challenges with enrollment due to recommendations for immunization of pregnant women in most participating countries, which may preclude them from reaching the full target enrollment for 700 subjects. As of August 13, 2021, enrollment included 259 subjects, and the sponsor anticipated enrollment for approximately 450 subjects by December 2021. The Sponsor's Internal Review Committee met on August 5, 2021, to review reactogenicity and safety data through 7 days after the second dose and recommended that the study continue. At this time, Pfizer plans (b) (4)

Upon further discussion between OVR and OBE, it was decided not to include the RCT in pregnant women as a PMC at this time. The study will continue under IND. OBE defers to OVR as the lead reviewer for this clinical trial.

- The SWG had concurred on the need for PMR(s) to further assess subclinical myocarditis, but additional details on study design were not available at the time of the SWG meeting. Since the SWG meeting, OVR had further communication with the sponsor and, the sponsor proposed protocol modifications to two clinical trials (studies C4591007 and C4591031) to assess subclinical myocarditis. OBE defers to OVR as the lead reviewer for these clinical trial PMRs:
  - A prospective assessment of the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age enrolled in Study C4591007

<sup>8</sup> The pregnancy registry will be in collaboration with the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry. The final protocol was submitted on July 1, 2021, is currently under review.

<sup>9</sup> [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)

- Study C4591031 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
- OBE and OVRP are in agreement with the following PMC for a vaccine effectiveness study: Study C4591014, entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California.” DE defers to OBE/IOD as the lead reviewer of real-world evidence (RWE) for vaccine effectiveness.
- OVRP included the following clinical trial as a PMC: An evaluation of the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age enrolled in Study C4591007. OBE defers to OVRP as the lead reviewer for this clinical trial PMC.

## 6 DE Recommendations

Should the product be approved, based on the review of the clinical trial safety data, and the post-authorization safety data, OBE/DE recommends the following pharmacovigilance activities:

- **Routine pharmacovigilance** in accordance with adverse event reporting regulations under 21 CFR 600.80, as per sponsor's proposed PVP (version 1.1).
- **Postmarketing requirement (PMR) safety studies** under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis:
  1. Study C4591009, entitled “A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.
  2. Study C4591021, entitled “Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.
  3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.
  4. 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).



The following clinical trials to assess subclinical myocarditis will be under the lead review of OVR:

5. A prospective assessment of the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age enrolled in Study C4591007.
  6. Study C4591031 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.
- **Postmarketing commitment (PMC) safety studies** agreed upon by FDA and applicant:
    1. Study C4591022, entitled “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.”
    2. Study C4591012, entitled “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.”
  - **Voluntary postmarketing studies:** The sponsor has agreed to provide updates regarding post-EUA studies that continue as voluntary studies post-licensure in periodic safety update reports (PSURs).
    1. C4591011: *Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization*
    2. 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*

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 approval letter for study milestone dates.

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.