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

# REAL WORLD EVIDENCE BLA MEMORANDUM

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| **From**: | Yun Lu, PhD<br>Mathematical Statistician<br>Analytics and Benefit-Risk Assessment Team (ABRA)<br>Office of Biostatistics and Epidemiology (OBE)<br>CBER, FDA |
| **To**: | Ramachandra Naik, PhD<br>Chair of the Review Committee<br>Office of Vaccines Research and Review |
| **Through**: | Richard Forshee, PhD<br>Acting Deputy Director, OBE<br>CBER, FDA |
| **Subject:** | Review of Pharmacovigilance Plan, Real World Post-Authorization Effectiveness Protocol C4591014, Post-Authorization Safety Protocols C4591009, C4591021, Amendment 30, Amendment 42, Amendment 51 |
| **Sponsor**: | BioNTech RNA Pharmaceuticals GmbH/Pfizer, Inc. |
| **Product**: | COMIRNATY; Pfizer-BioNTech COVID-19 Vaccine* |
| **Application Type/Number**: | BLA STN 125742/0 |
| **Proposed Indication:** | Prevention of COVID-19 in individuals 16 years of age and older |
| **Submission Date**: | May 18, 2021 |

*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 real world post-authorization vaccine effectiveness protocols C4591014, post-authorization vaccine safety protocols C4591009 and C4591021 for Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine COMIRNATY.

Materials Reviewed

- Pharmacovigilance Plan, Version 1.1 (STN 125742/0.20; received July 29, 2021)
- Response to CBER 28 July 2021 Information Request Regarding Post-marketing Safety Study(ies) (STN 125742/0.30; received August 3, 2021)
- Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies (STN 125742/0.42; received August 11, 2021)
- Response to CBER 13 August 2021 Information Request Regarding Safety-Related Postmarketing Requirement/Postmarketing Commitment Studies (STN 125742/0.51; received August 16, 2021)
- C4591009 Synoposis: A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States.
- C4591021 protocol: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
- C4591014 protocol: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California

## 2 PRODUCT INFORMATION

### 2.1 Product Description

The Pfizer-BioNTech COVID-19 Vaccine COMIRNATY contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). 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

The proposed indication for Pfizer-BioNTech COVID-19 Vaccine COMIRNATY in the United States is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

## 3 POST-AUTHORIZATION SAFETY AND EFFECTIVENESS STUDIES

In Response to CBER 28 July 2021 Information Request Regarding Post-marketing Safety Study(ies) (STN 125742/0.30; received August 3, 2021), the sponsor provided required number of cases to detect Myocarditis risk under

different assumptions of background rates. The sponsor also compared four post-authorization safety studies C4591009 (US), C4591011 (US), C4591012 (US), and C4591021(EU) to assess increased risk of safety events of interest, including myocarditis/pericarditis.

*Reviewer comment:* *Among the four proposed post-authorization safety studies, two studies C4591009 (US) and C4591021(EU) have relatively large source population. The estimated number of individuals ≤30 years administered Pfizer vaccine is approximately 14.1 million in C4591009 and approximately 4.1 million in C4591021. It would be useful to include these two safety studies as postmarketing requirements (PMRs).*

*Please provide protocols for the C4591021 study and C4591021 substudy.*

*The sponsor submitted C4591009 protocol synopsis, and the protocol is expected to be finalized by August 31, 2021.*

*Below are the comments for C4591009 protocol synopsis:*

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.*

In Response to CBER 10 August 2021 Information Request Regarding Post-marketing Safety Studies (STN 125742/0.42; received August 11, 2021), the sponsor addressed questions regarding study C4591009 and provided protocol for study C4591021.

*Reviewer comment:*

*Below are the comments for sponsor's response regarding C4591009(US):*

1. *The sponsor addressed exposure misclassification issue in the full C4591009 protocol (to be submitted by August 31, 2021) with pre-specified feasibility assessment. If vaccine coverage estimates differ meaningfully from the "benchmarking" estimates, the sponsor may consider the SCRI or the cohort design with historical unexposed comparators as the primary study designs and/or consider linkage to immunization registries if feasible.*

   *The sponsor's response is acceptable.*

   *The COVID pandemic could have short-term and long-term impact on people's health seeking behavior. For historical unexposed comparators, please clarify how you plan to evaluate the temporal trend of time varying confounders.*

   *Page 12 of the C4591009 protocol synopsis mentioned ICD-9-CM and ICD-10-CM codes. ICD-10-CM was effective as of Oct 1, 2015. Please clarify whether historical unexposed comparators before Oct 1, 2015 will be used. There are differences between the ICD-9-CM and ICD-10-CM codes, and bias could be introduced. Please clarify how you plan to address the differences between the ICD-9-CM and ICD-10-CM system.*

2. *The length of the control window in the SCRI analyses will be assessed separately for each outcome and the risk intervals for each safety event of interest will be provided in Section 9.3.2.1 of the full C4591009 protocol.*

   *The sponsor's response is acceptable.*

3. *The sponsor will incorporate a 7-day risk period for myocarditis into the protocols.*

   *The sponsor's response is acceptable.*

4. *The sponsor provided study size estimates for 1:1 matching for true RR=1, 1.2 and 1.4 in Appendix 1.*

   *The sponsor's response is acceptable.*

*The sponsor submitted C4591021(EU) protocol. Below are the comments:*

1. *Page 21. Section 9.1.1.1. Matching process.*

   *The sponsor proposed "a 1:1 matching without replacement using a 'rolling cohort' design". A vaccinated individual will be censored if his/her unvaccinated match is vaccinated later.*

   *If rapid vaccine rollout happens and a large number of individuals receive vaccines within a short period of time, many vaccinated individuals may get censored. This will have a negative impact on the person time. Please clarify how you plan to address this potential issue.*

2. *Page 23. Section 9.1.2. Self-controlled risk interval (SCRI) design.*

   *Figure 1 illustrated a SCRI example with a risk window of 42 days and a control window of 42 days. Please clarify how the risk interval and control interval are defined for a fully vaccinated individual. For example, for a person who receives the 2nd dose 21 days after the 1st dose, the 1st dose and the 2nd dose risk intervals overlap. Is the risk window 42 days or 42+21=63 days? Is the control window 42 days or 42+21=63 days?*

3. *Page 29. Section 9.3.2.1. Safety outcomes*

   *Table 1, Heparin-induced thrombocytopenia (HIT)–like event has a risk interval of 15 days. For a person who receives the 2nd dose 21 days after the 1st dose, the 1st dose risk interval and the 2nd dose risk interval do not overlap. Please clarify the HIT-like event risk and control windows for people who receive two doses.*

4. *Page 29. Section 9.3.2.1. Safety outcomes*

   *Table 1. Cardiovascular system. Myocarditis is one of the AESIs. The risk window was listed as "any". Please specify the length of risk window for myocarditis. Only cohort study was proposed in the Table. Please consider adding SCRI for myocarditis.*

5. *Page 32, 9.3.3. Covariate definition*

   *"Age will be categorised as age categories in line with published background incidence rates from ACCESS (0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+)"*

*Myocarditis is one of the AESIs. Please consider refining the age category 0-19 to include an adolescent age group, such as 10-19 years old.*

6. *Page 47, 9.5. Study size*

   *The protocol mentioned that "The study will be conducted in a source population of 38.9 million individuals captured in the electronic healthcare data sources."*

   *Seven data sources are included in the protocol with a total source population of 38.9 million. The data will be analyzed separately by data source. The number of active individuals ranges from 1 million in Pedianet/Health Search Database (IT) to 16 million in Clinical Practice Research Datalink and Hospital Episode Statistics (UK). Some data sources may not have enough study size to detect rare AESIs.*

In the Pharmacovigilance Plan, the Sponsor planned three real world post-authorization vaccine effectiveness studies to determine the effectiveness of COMIRNATY when administered outside of the clinical setting: one non-interventional study C4591014 and two low-interventional studies WI235284 and WI255886.

*Reviewer comment:*

*WI235284 COVID-19 vaccine effectiveness (VE) Substudy 6 will enroll healthy women who present at Emory University Hospital or Emory University Hospital Midtown for delivery, regardless of respiratory syncytial virus or COVID-19 status. A test negative case-control design is proposed.*

*Study WI255886 will be conducted in Bristol, England with approximately 630,000 adults in surveillance population. Real world VE estimates for COVID-19 vaccines will be assessed using a test negative design case control analysis.*

*Study C4591014 will estimate the VE of 2-doses of Pfizer's COVID-19 vaccine against acute respiratory illness requiring hospitalization due to SARS-CoV-2 infection among Kaiser Permanente Southern California (KPSC) members ≥16 years of age. Two parallel study designs are proposed: a test-negative case-control design and a retrospective cohort design.*

*Among the three proposed real world post-authorization vaccine effectiveness studies, Study C4591014 has the largest source population. KPSC has significant proportions of adolescent and young adult populations. It would be useful to include this effectiveness study as a postmarketing commitment (PMC) and include individuals 12 through 15 years of age.*

In Response to CBER 13 August 2021 Information Request Regarding Safety-Related Postmarketing Requirement/Postmarketing Commitment Studies (STN 125742/0.51; received August 16, 2021), the sponsor addressed questions regarding study C4591014.

*Reviewer comment:*

*The sponsor agreed to include individuals 12 through 15 years of age in Study C4591014.*

*The sponsor's response is acceptable.*

## 4 OBE REAL WORLD EVIDENCE RECOMMDENDATIONS

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, using real world evidence study design:

1. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States."
2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."
3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

OBE will review the final protocols for C4591009 and C4591021 substudy when available (please see approval letter for study milestone dates). The final protocol for Study C4591021 was submitted August 11, 2021 [under STN 125742.0.42] and is currently under review[1].

Postmarketing commitment (PMC) vaccine effectiveness study agreed upon by FDA and the sponsor:

1. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California." Include individuals 12 through 15 years of age.

Note that PMR/PMC studies, in addition to the above listed studies, have been described in OBE/Division of Epidemiology pharmacovigilance plan (PVP) review memo and addendum memo.

[1] Note that the FDA review for this protocol will be documented in a separate protocol review memorandum. Additionally, study C4591021 is also a post-conditional approval study for the European Medicines Agency (EMA) and the protocol was approved by the EMA on June 24, 2021.