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Global Product Development

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Marion Gruber, Ph.D.
Director
Office of Vaccines Research and Review
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
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SN 0469

Re: COVID-19 Vaccine (BNT162/PF-07302048) BB-IND 19736

IND Amendment –

- **Protocol Amendment for Study C4591012**
- **New Study C4591009 Protocol**

Dear Dr. Gruber,

Reference is made to BB-IND 19736 for the COVID-19 Vaccine (BNT162; PF-07302048), which Pfizer and BioNTech are developing for the indication of active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The IND was effective on 29 April 2020 and the Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 Vaccine issued on 23 August 2021.

Reference is also made to the Post-Authorization Safety Study (PASS) 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*" submitted to the BB-IND 19736 (SN 0195) and EUA 27034 on 29 January 2021.

The present submission provides C4591012 Clinical Protocol Amendment 1 (version 2.0), Clean copy and Tracked change copy.

Protocol Amendment 1 includes the following key changes:

- Section 6: Updated the Milestones section.

- Section 9.1.1:
    - Added clarification on the self-controlled risk interval (SCRI) design, including a description of the measurements when there is a gap between risk intervals for the first and second dose and an illustration (new Figure 2B).
    - Added that additional doses of the Pfizer-BioNTech COVID-19 vaccine may be included in the analysis.
- Sections 9.1.1, 9.3.3, 9.7.3, 9.7.5 and 9.9:
    - Removed SCRI design with pre-vaccination control interval and added SCRI design with post-vaccination control interval for 2 safety events of interest (severe COVID-19, multisystem inflammatory syndrome in adults [MIS-A]) that could not be evaluated with the seasonal influenza vaccinated comparators.
    - Revised Figures 1-5 to remove pre-vaccination control interval and provide examples for post-vaccination interval.
- Sections 9.2.3 and 9.4:
    - Added clarification for the identification of subgroups who are immunocompromised s and individuals with specific comorbidities.
    - Added one additional subgroup of interest (individuals with Medicare coverage for whom Veterans Health Administration [VHA] records can be linked to their Medicare claims).
- Section 9.3.1: All measurement details concerning how Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine will be identified in the data to an Appendix Table 3 in Section 18. Appendix Table 3 includes all specific CPT/HCPCS/NDC codes previously listed in Section 9.3.1 as well as additional codes identified at the time of the data analysis.
- Sections 9.3.1 and 18: Added Appendix Table 4 in Section 18 regarding the LOINC codes used to identify COVID-19 RT-PCR Test among the study population and corresponding reference.
- Sections 9.3.2 and 18: Added frailty index as a baseline characteristic of interest.
- Sections 9.3.3 and 18:
    - Added four additional safety events of interest: thrombosis with thrombocytopenia syndrome, convulsions/seizures in individuals with controlled epilepsy, Steven-Johnson syndrome/Toxic epidermal necrolysis, and hemolytic anemia (increasing the number of safety events of interest from 42 to 46).
    - Reclassified COVID-19-related safety events of interest to be measured independently of the patient's COVID-19 infection status; this change had no impact on the number of safety events of interest (reflected both in the revised text and revised Table 1).
    - Added that the clean window may be extended (e.g., 2 years).
- Section 9.7.3.2: Clarified in the Signal Evaluation section that the signal evaluation analyses will be conducted every six months.
- Sections 9.1.3 and 9.7.3.2.5: Added self-controlled case series (SCCS) design with full post-vaccination period as an additional analysis in the Signal Evaluation analysis. Added that Signal Evaluation analyses may also be conducted based on

signals detected in external sources or based on regulatory request (e.g., myocarditis/pericarditis).
- Section 9.7.3.2.6: Added a comparison group of contemporary unvaccinated controls in the Signal Evaluation analysis.
- Section 9.7.8: Added new section on myocarditis/pericarditis safety analysis and risk factor analysis.
- Section 9.9: Added strengths and limitations associated with the addition of the SCCS design, contemporaneous unvaccinated controls, and subgroup analysis of individuals with linkage to Medicare claims data.

In addition, this submission also provides the final protocol for the new Post-Authorization Safety Study (PASS) C4591009 entitled, *"A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States"*. This study is planned to initiate in Q2 of 2022.

This is being submitted to both BB-IND 19736 and EUA 27034 in parallel.

This submission has been scanned for viruses using McAfee VirusScan Enterprise Version 8.8 and is virus free. The submission is being sent via the Gateway.

Should you have any questions regarding this submission, or require additional information, please contact me via phone at 214-918-5262 or via e-mail at Amitkumar.Patel@pfizer.com.

Sincerely,

Amit Patel
Director
Global Regulatory Affairs - Vaccines

CC: Ramachandra S. Naik, Ph.D.
CC: Laura Gottschalk, Ph.D.
CC: Captain Michael Smith, Ph.D.