U.S. FOOD & DRUG ADMINISTRATION

CMC REVIEW MEMORANDUM

Date: May 2, 2022

To: The Biologics License Application (BLA) File STN 125742

From: Xiao Wang, CMC Reviewer, OVRR/DVP

Xiao Wang -S (Affiliate) Digitally signed by Xiao Wang -S (Affiliate) Date: 2022.05.02 16:58:16 -04'00'

Through: Anissa Cheung, OVRR/DVP

Keith Peden, Lab Chief, OVRR/DVP

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Applicant: BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.)

Product: COMIRNATY; COVID-19 Vaccine, mRNA (BNT162b2)

Product Type: A Nucleoside-modified Messenger RNA (mRNA) Vaccine Encoding SARS-CoV-2 Spike Glycoprotein, Formulated with Lipids ALC-0315, ALC-0159, DSPC, and Cholesterol to form Lipid Nanoparticles (LNPs)

STN: STN 125742/45

Subject: Review of STN 125742/45 Prior Approval Supplement (PAS);

Clinical diagnostic and serological assays used in clinical study C4591001 in support of licensure expansion of COMIRNATY for active immunization in adolescents 12 through 15 years of age

Action Due Date: June 17, 2022

Materials Reviewed:

Date Received	Submission	Contents
December 16, 2021	STN 125742/45	• Section 2.5 Clinical overview – 12-15 years • Section 2.7.1 Summary of biopharmaceutic studies and associated analytical methods • VR-MVR-10080 Report on method validation of a Cepheid Xpert Xpress PCR assay to detect SARS-CoV-2

Date Received	Submission	Contents
		• VR-MVR-10083 Validation report for the SARS-CoV-2 mNeonGreen virus microneutralization assay • Section 16.1.10 Documentation of inter-laboratory standardization methods and quality assurance
January 28, 2022	STN 125742/45.1	Response to FDA information request (IR) regarding a claim for Categorical Exclusion (CE)

Executive Summary:

COMIRNATY (COVID-19 mRNA Vaccine) is a licensed vaccine indicated for active immunization for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals ≥ 16 years of age. In this sBLA submission, the applicant provided updated safety, efficacy, and immunogenicity data of the vaccine to support expansion of COMIRNATY licensure to include adolescents 12 through 15 years of age. Of note, the vaccine (also known as Pfizer-BioNTech COVID-19 vaccine, BNT162b2) has been authorized under Emergency Use Authorization (EUA) for emergency use in individuals ≥ 12 years of age.

The COMIRNATY vaccine is currently approved to be formulated in either PBS/Sucrose or Tris/Sucrose buffer, both at the 30-µg RNA dose, for individuals ≥ 16 years of age. This sBLA intends to extend licensure of COMIRNATY to adolescents 12 through 15 years of age for both the PBS/Sucrose and Tris/Sucrose formulations. The 30-µg dose of the vaccine is approved for use as a 2-dose primary series administered 21 days apart.

This memo focuses the clinical assays used for immunogenicity and efficacy analyses in clinical Phase 1/2/3 Study C4591001 in support of COMIRNATY licensure expansion in adolescents 12 through 15 years of age. For clinical efficacy endpoint confirmation, a SARS-CoV-2 PCR assay (Cepheid Xpert Xpress RT-PCR assay, FDA-authorized under EUA) was used to confirm COVID-19 cases in the central laboratory. For immunogenicity analysis, a neutralization assay, SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), was used to evaluate immune response of the participants. To support the proposed indication to include adolescents (12 through 15 years of age), immunobridging analyses were performed to demonstrate noninferiority (NI) of immune response to the vaccine in participants 12 to 15 years of age compared with young adults 16 to 25 years of age. Both the Cepheid Xpert Xpress RT-PCR assay and SARS-CoV-2 mNG NT have been described and validated for evaluation of clinical samples in the original BLA application for COMIRNATY; the BLA was approved on August 23, 2021.

Recommendation:

The validated Cepheid Xpert Xpress RT-PCR assay and SARS-CoV-2 mNG NT assay are suitable to be used for the analysis of clinical samples in support of the expansion of COMIRNATY licensure to include adolescents 12 through 15 years of age.

Submission and Review:

Efficacy Endpoints and Analysis Methods

Clinical efficacy endpoint in Study C4591001 was assessed based on confirmed cases of COVID-19 in the efficacy populations. COVID-19 case determination involves testing at a central laboratory using a validated reverse transcription-polymerase chain reaction (RT-PCR) test (Cepheid Xpert Xpress assay, EUA 200047/A001). If a central laboratory result was not available, a local NAAT result was considered acceptable only if it was performed according to the validated protocol and met protocol-specified criteria.

Efficacy Analysis Method – Cepheid Xpert Xpress RT-PCR Assay

The Cepheid Xpert Xpress SARS-CoV-2 assay is a rapid, automated *in vitro* diagnostic test for the qualitative detection of the nucleocapsid (N) and envelope (E) gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/ aspirate specimens collected from patients suspected of having COVID-19 disease. The Cepheid Xpert assay was used to assess viral infection before vaccination and to confirm COVID-19 disease cases during study follow-up. The assay has previously been validated by evaluating parameters of accuracy and detection limit (refer to EUA 27034 and BLA 125742 review memos regarding assay description and validation results). The validation results support its intended use for efficacy endpoint evaluation in Pfizer's clinical trial of the BNT162b2 vaccine.

Efficacy Results – Participants 12 Through 15 Years of Age

In the current PAS submission, updated efficacy analyses include COVID-19 cases in the 12-15 years of age group accrued in blinded follow-up to a data-cutoff date of September 2, 2021. The total evaluable efficacy population with or without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2 includes 1119 participants in the BNT162b2 vaccine group and 1109 participants in the placebo group.

In the adolescent group, the observed vaccine efficacy (VE) against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100% (0 and 28 cases in the BNT162b2 and placebo group, respectively, with 2-sided 95% CI: 86.8%, 100%) for individuals without evidence of SARS-CoV-2 infection before and during vaccination regimen, and 100% (0 and 30 cases in the BNT162b2 and placebo group, respectively, with 2-sided 95% CI: 87.5%, 100%) for those with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The efficacy analysis for the dose 1 all-available population included 3 cases in the BNT162b2 group and 48 cases in the placebo group, with an observed VE of 94.0% (2 sided 95% CI: 81.3%, 98.8%).

Among the 30 placebo participants who had COVID-19 cases, most variants sequenced were neither a Variant of Interest (VOI) nor a Variant of Concern (VOC) except for the B.1.1.7 (Alpha) variant found in 23.3% of placebo participants. It is worth noting that all of the cases in the efficacy analyses occurred between November 2, 2020, to May 19, 2021, which is before the Delta surge in the US.

Immunogenicity Endpoints and Analysis Methods

To support COMIRNATY licensure expansion to include adolescent 12-15 year of age, one immunogenicity objective was to demonstrate noninferiority (NI) of the immune response to BNT162b2 in participants 12-15 years of age compared with participants 16-25 years of age who had no evidence of past SARS-CoV-2 infection. A validated SARS-CoV-2 neutralization assay (SARS-CoV-2 mNeonGreen virus microneutralization assay) was used for the immunobridging analysis between the younger adolescents and young adults 16-25 years of age.

SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (SARS-CoV-2 mNG NT)

The SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT) was developed and used in the Phase 2/3 study C4591001 to measure neutralizing antibodies against the reference strain in clinical serum samples. The assay is based on a recombinant USA_WA1/2020 strain engineered to contain an mNeonGreen (mNG) reporter gene, which produces a green-fluorescent signal as a read-out for virus infectivity. The neutralization titer (NT50) of the serum samples was defined as the reciprocal serum dilution at which 50% of the virus infectivity is eliminated. The SARS-CoV-2 mNG NT has been described previously for evaluations of clinical samples in the original BLA application for COMIRNATY; the BLA was approved on August 23, 2021.

The SARS-CoV-2 mNG NT assay has been validated using both vaccinee and (b) (4) serum samples at Hackensack Meridian Health located at Nutley, NJ, USA. The evaluated assay qualification/validation parameters include precision (b) (4) intermediate precision), dilutional linearity, (b) (4) detection limit, quantification limit, and extravariability of replicates (refer to the BLA 125742 review memo for details regarding the assay description and assay validation). The validation results demonstrate that the assay is suitable for the assessment of neutralizing antibodies against the original USA_WA1/2020 strain.

Immunogenicity Results - Participants 12 Through 15 Years of Age

Geometric Mean Ratio (GMR) in Neutralization Titers (NT50)

Noninferiority (NI) was assessed based on the GMR of SARS-CoV-2 neutralizing titers at 1 month after Dose 2 in participants (adolescents vs. young adults) without prior evidence of SARS-CoV-2 infection. The GMT ratio of adolescents to young adults was 1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5 fold NI criterion (i.e. lower bound of the 2-sided 95% CI for GMR > 0.67). Of note, the lower bound of the 2-sided 95% CI for the GMR is > 1 which indicates a statistically greater response in the adolescents than that of young adults.

Seroresponse

Among participants without evidence of SARS-CoV-2 infection up to 1 month after Dose 2 of BNT162b2, high proportions (97.9% of adolescents and 100.0% of young adults) had a ≥ 4-fold rise (seroresponse) in SARS-CoV-2 NT50 at 1 month after Dose 2 compared with

pre-vaccination, with a seroresponse rate difference of -2.1%.

In conclusion, the immunobridging success criteria were met based on the GMRs and seroresponse rates for the reference USA_WA1/2020 strain. The vast majority of BNT162b2 recipients in both age group achieved ≥ 4-fold rise in SARS-CoV-2 NT50 at 1 month after Dose 2 compared with pre-vaccination.

Reviewer's Comment:

The submitted immunobriding analyses were based on an assay limit of detection (LOD) of 20. New analyses using the validated lower limit of quantification (LLOQ) of 41 were performed. The results show that the GMR, previously 1.76 (95% CI: 1.47, 2.10) is now 1.77 (95% CI: 1.50, 2.09), and the seroresponse rate difference, previously -2.1% is now 0.4%. These changes have no impact on the conclusions of the immunogenicity results.

Reviewer's Final Comments and Conclusions:

- Both the Cepheid Xpert Xpress RT-PCR assay (EUA 200047/A001) as a diagnostic assay for the detection of SARS-CoV-2 infection and SARS-CoV-2 mNG NT assay as a serological assay for the assessment of neutralizing antibody titers to the BNT162b2 vaccine in clinical samples for study C4591001 have been successfully validated. Both assays are suitable for their intended purposes for analyzing clinical samples to support expansion of COMIRNATY licensure in adolescents 12-15 years of age.
- The current PAS submission presents updated safety, efficacy, and immunogenicity data for adolescents 12-15 years of age up to the data cutoff date (September 2, 2021). VE after 7 days post Dose 2 was high (100%) in participants 12-15 years of age without and with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen, and the data support efficacy of the BNT162b2 vaccine in adolescents. The immunogenicity data demonstrated that the immune response elicited by 30 µg of BNT162b2 in adolescents 12-15 years of age was noninferior to the immune response in young adults 16-25 years of age. However, I defer to the clinical and biostatistics reviewers on the final decision regarding the acceptability of updated clinical data.
- The applicant submitted a claim of categorical exclusion (CE) to the environmental assessment and stated that the use of COMIRNATY for the prevention of COVID-19 disease in adolescents 12-15 years of age does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The active ingredient is recognized as naturally occurring substance, and no extraordinary circumstances exist. The claim is considered acceptable.