U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)

REAL WORLD EVIDENCE sBLA MEMORANDUM

From:

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To:

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Through:

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Subject: Review of Clinical Overview, Pharmacovigilance Plan, real world vaccine effectiveness studies against Omicron variant among adolescents

Sponsor: BioNTech RNA Pharmaceuticals GmbH/Pfizer, Inc.

Product: COMIRNATY; Pfizer-BioNTech COVID-19 Vaccine*

Application Type/Number: sBLA STN 125742/45

Proposed Indication: Prevention of COVID-19 in individuals 12 years of age and older

Submission Date: December 16, 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 evidence for supplemental Biologics License Application (sBLA) 125742/45, which proposes to extend use of Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine COMIRNATY to adolescents 12 through 15 years of age from the current 16 years of age and older licensed indication.

Materials Reviewed

- Clinical Overview (STN 125742/45; received December 16, 2021)
- Pharmacovigilance Plan version 1.4.1 (STN 125742/45.9; received May 2, 2022)
- COMIRNATY approval letter (STN 125742/0; dated August 23, 2021)
- Real world effectiveness studies of Pfizer-BioNTech COVID-19 Vaccine against Omicron variant among adolescents (published on or before May 13, 2022)
- C4591014 protocol amendment 2: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California (IND 19736.597; received December 13, 2021)
- Combined statistical analysis plan (SAP) for studies C4591014, WI235284 and WI255886 (IND 19736.597; received December 13, 2021)

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 12 years of age and older.

3 REAL WORLD EFFECTIVENESS STUDIES

In the Clinical Overview (STN 125742/45; received December 16, 2021), the sponsor referenced six vaccine effectiveness (VE) publications containing real-world data from Israel and the United States. The sponsor stated that “Overall, real-world effectiveness data to date indicate high VE against infection and hospitalization following two doses of BNT162b2 in individuals 12-15 years of age of approximately 90%.”

Reviewer comment: The six real world effectiveness (VE) studies in the Clinical Overview were all from pre-Delta or Delta predominant periods.[1-6] Since the first Omicron variant COVID-19 case in the United States on December 1, 2021, Omicron quickly became the predominant strain in the United States. Real world VE studies in the Omicron predominant period are more relevant to this sBLA.

As of May 19, 2022, several publications investigated real world VE of Pfizer-BioNTech COVID-19 BNT162b2 vaccine among adolescents during the Omicron predominant period.

A prospective cohort study evaluated effectiveness of 2-Dose BNT162b2 in preventing SARS-CoV-2 infection July 2021-February 2022 in four states.[7] Among adolescents aged 12-15 years, adjusted VE 14-149 days after dose 2 was 87% (95% CI = 49%-97%) and 59% (95% CI = 22%-79%) against Delta and Omicron infection, respectively.

A test-negative case-control study investigated VE against emergency department (ED) and urgent care (UC) encounters April 2021-January 2022 in ten states.[8] Among adolescents aged 12-15 years, estimated VE 14-149 days after dose 2 of BNT162b2 was 92% (95% CI = 89%-94%) and 45% (95% CI = 30%-57%) against COVID-19-associated ED and UC encounters during Delta and Omicron predominant periods, respectively. Estimated VE ≥150 days after dose 2 decreased to 79% (95% CI = 68%-86%) and −2% (95% CI = −25%-17%) during Delta and Omicron predominant periods, respectively.

A test-negative case-control study investigated VE against laboratory-confirmed COVID-19 leading to hospitalization (COVID-19 hospitalization) and against COVID-19 leading to receipt of life support or to death (critical COVID-19) July 2021-February 2022 in 23 states.[9] Among adolescents 12-18 years of age during the Omicron predominant period, estimated VE of BNT162b2 was 40% (95% CI, 9%-60%) against COVID-19 hospitalization, 79% (95% CI, 51%-91%) against critical COVID-19, and 20% (95% CI, −25%-49%) against noncritical COVID-19.

Another study included a total of 22,273 test-positive COVID-19 cases and 25,471 test-negative controls from adolescents 12-15 years of age December 2021-February 2022 during Omicron predominant period across the United States.[10] At 2 to 4 weeks after dose 2 of BNT162b2, the estimated VE against symptomatic COVID-19 infection was 59.5% (95% CI, 44.3%-70.6%). During month 2 after dose 2, the estimated VE decreased to 16.6% (95% CI, 8.1%-24.3%). The estimated VE 2 to 6.5 weeks after the booster dose was 71.1% (95% CI, 65.5%-75.7%).

These recently published real world VE studies among adolescents showed decreased VE of 2-Dose BNT162b2 during Omicron predominant period than Delta predominant period, higher VE against critical COVID-19 than noncritical COVID-19, potential waning effectiveness, and better protection of the booster dose.

In Pharmacovigilance Plan, the sponsor stated "Four post-authorization effectiveness studies in real-world use are ongoing: 1 interventional study (BNT162-01 cohort 13), 1 non-interventional study (C4591014) and 2 low-

interventional studies (WI235284 and WI255886) to determine the effectiveness of BNT162b2 when administered outside of the clinical setting."

Reviewer comment: The non-interventional study (C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California") was postmarketing commitment (PMC) #13 of BLA 125742/0. The study included individuals 12-15 years of age. The amended protocols and combined statistical analysis plan (SAP) for studies C4591014, WI235284 and WI255886 were submitted to IND 19736.597 (received December 13, 2021), and the documents are acceptable.

4 OBPV REAL WORLD EVIDENCE RECOMMDENDATIONS

Should the product be approved in individuals 12-15 years of age, based on the review of the published real world vaccine effectiveness studies among adolescents, OBPV recommends the following action:

Postmarketing commitment (PMC) vaccine effectiveness study as outlined in the BLA 125742/0 approval letter: Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California." The study included individuals 12 through 15 years of age.

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