Clinical Review Memorandum Addendum to an Emergency Use Authorization (EUA) for an Unapproved Product

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27034, Amendments 636 and 658
Sponsor	Pfizer, Inc.
Submission Date	September 8, 2022
Receipt Date	September 8, 2022
Primary Clinical Reviewer	Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA
Supervisory Concurrence	Lucia Lee, M.D., Team Lead, OVRR/DVRPA
Review Completion Date	November 18, 2022
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension (3 µg BNT162b2) for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 6 months through 4 years of age

Executive Summary

Comirnaty (BNT162b2) is licensed for active immunization to prevent Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Emergency Use Authorizations (EUA) of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for use in individuals 5 through 11 years of age and individuals 6 months through 4 years of age were granted on October 29, 2021 and June 17, 2022, respectively. Safety and effectiveness data supporting approval of Comirnaty and EUA of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

Pfizer submitted EUA amendment 636 (EUA 27034.636) on September 8, 2022 to revise the Fact Sheets with updated descriptive vaccine efficacy (VE) results from the ongoing, randomized, double-blinded, placebo-controlled trial C4591007, following a 3-dose BNT162b2 primary series in participants 6 months through 4 years of age, using a June 17, 2022 data cutoff. Study participants 6 months through 4 years of age were randomized 2:1 to receive 2 doses of either BNT162b2 at 3 µg mRNA per dose or saline placebo, administered 3 weeks apart. Following analysis of the post-Dose 2 safety and effectiveness data, the protocol was amended to administer a third primary series dose to participants 6 months through 4 years of age at least 8 weeks after Dose 2. Participants were surveilled for cases of confirmed COVID-19.

A total of 3793 BNT162b2 recipients and 1891 placebo recipients 6 months through 4 years of age [1444 BNT162b2 recipients and 718 placebo recipients 6 months through 23 months (hereafter 6-23 months) of age and 2349 BNT162b2 recipients and 1173 placebo recipients 2 years through 4 years (hereafter 2-4 years) of age] received at least one dose of the study product in the Phase 2/3 portion of Study C4591007 at the time of the June 17, 2022, data cutoff. Vaccine efficacy was assessed in a total of 873 BNT162b2 recipients and 381 placebo recipients 6 months through 4 years of age (554 BNT162b2 recipients and 224 placebo recipients 2-4 years of age and 319 BNT162b2 recipients and 157 placebo recipients 6-23 months of age) who were included in VE analysis population, the Dose 3 evaluable efficacy population without evidence infection prior to 7 days after Dose 3. The median length of blinded efficacy follow-up post-Dose 3 was 1.9 months for participants 6-23 months of age and 2.4 months for participants 2-4 years of age in the VE analysis population.

As of the June 17, 2022, data cutoff, vaccine efficacy was 73.2% (95% CI: 43.8%, 87.6%) against protocol-defined COVID-19 in participants 6 months through 4 years of age without evidence of infection up to 7 days post-Dose 3. Similar VEs were observed within each age group (6-23 months and 2-4 years) and among participants with or without evidence of infection. One severe COVID-19 case occurred in a placebo recipient in the 6–23-month age group, which met criteria due to an increased heart rate in the context of fever and did not require hospitalization. No cases of multisystem inflammatory syndrome in children were reported through the June 17, 2022 data cutoff date.

Pfizer submitted EUA amendment 658 (EUA 27034.658) on September 10, 2022 to revise the Fact Sheets to add dizziness. Review of the Sponsor's safety data and VAERS data showed that dizziness is one of the most frequently reported adverse events following vaccination with the Pfizer-BioNTech COVID-19 Vaccines (monovalent and bivalent) in the post-authorization setting.

FDA Review of Updated BNT162b2 Primary Series Vaccine Efficacy Data

The EUA amendment 636 contains updated BNT162b2 vaccine efficacy (VE) data following 3 primary series doses in Study C4591007 Phase 2/3 participants 6 months through 4 years of age. Additional details of the study design, immunogenicity results, preliminary vaccine efficacy results, safety results, and benefit/risk considerations for granting the authorization of Pfizer-BioNTech COVID-19 Vaccine for use in individuals 6 months through 4 years of age are described in the Division Review Memorandum. This clinical review memorandum will focus on the updated vaccine efficacy results to be included in the Fact Sheets.

Study C4591007 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study in children 6 months through 11 years of age, although only VE data from participants 6 months through 4 years of age are presented here. The study originally randomized participants 2:1 to receive 2 doses of BNT162b2 or placebo 3 weeks apart. Following post-Dose 2 safety and effectiveness analyses, the study was amended to include Dose 3 at least 8 weeks after Dose 2 because the immunobridging success criteria were not met for participants 2-4 years of age.

Participants were surveilled for cases of confirmed COVID-19. The case definition for a confirmed case of COVID-19 was the presence of at least one of the following symptoms and a positive SARS-CoV-2 nucleic acid amplification test (NAAT) within 4 days of the symptomatic period: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting, inability to eat/poor feeding. Positive COVID-19 NAAT cases confirmed by the central laboratory or valid local test also underwent BioFire testing for coinfection with other respiratory pathogens.

VE was estimated based on confirmed COVID-19 cases observed at least 7 days post-Dose 3 in the Dose 3 evaluable efficacy population, defined as participants who received all 3 doses of the randomized investigational product within the predefined window during blinded follow-up and had no other important protocol deviations.

In addition, VE against severe COVID-19 was evaluated in the Dose 1 all-available efficacy population, which included all participants who received at least one dose of the investigational product. Severe COVID-19 was defined as a confirmed COVID-19 case, plus at least one of the following: clinical signs at rest indicative of severe systemic illness (based on age-specific respiratory and heart rates[1], SpO_2 ≤92% on room air or >50% FiO_2 to maintain ≥92%, or PaO_2/FiO_2 <300 mm Hg); respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); evidence of shock or cardiac failure (systolic blood pressure outside of the age-specific range); significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; death.

Disposition

The Dose 1 all-available efficacy population included 3793 BNT162b2 recipients and 1891 placebo recipients 6 months through 4 years of age, as of the June 17, 2022 data cutoff date. The populations of participants 6 months through 4 years of age who received 3 doses of study intervention were as follows:

- Dose 3 all-available efficacy population: 1351 BNT162b2 recipients and 642 placebo recipients
- Dose 3 evaluable efficacy population with or without evidence of prior SARS-CoV-2 infection: 1294 BNT162b2 recipients and 612 placebo recipients

- Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection: 873 BNT162b2 recipients and 381 placebo recipients (analysis population used for VE assessments).

The median duration of blinded follow-up was 2.2 months for participants 6 months through 4 years of age in the Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection.

Participants 6-23 months of age
The Phase 2/3 Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection for participants 6-23 months of age included 319 BNT162b2 recipients and 157 placebo recipients, and the median duration of blinded follow-up after Dose 3 was 1.9 months. As shown in Table 1, a total of 957 (66.3%) and 481 (67.0%) participants were excluded from the BNT162b2 and placebo groups, respectively, due to not receiving Dose 3 prior to unblinding.

Table 1. Disposition of Participants 6-23 Months, Phase 2/3 Efficacy Population, Study C4591007

Disposition, n (%)	BNT162b2 3 µg N=1444	Placebo N=718	Total N=2162
Dose 1 all-available efficacy population	1444 (100.0)	718 (100.0)	2162 (100.0)
Dose 3 all-available efficacy population	487 (33.7)	237 (33.0)	724 (33.5)
Participants excluded from Dose 3 all-available efficacy population	957 (66.3)	481 (67.0)	1438 (66.5)
Did not receive 3 vaccinations prior to unblinding	957 (66.3)	481 (67.0)	1438 (66.5)
Dose 3 Evaluable efficacy population	474 (32.8)	229 (31.9)	703 (32.5)
Participants without evidence of infection prior to 7 days after Dose 3	319 (22.1)	157 (21.9)	476 (22.0)
Participants excluded[a] from Dose 3 evaluable efficacy population	970 (67.2)	489 (68.1)	1459 (67.5)
Did not receive all vaccinations as randomized prior to unblinding	957 (66.3)	481 (67.0)	1438 (66.5)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	26 (1.8)	10 (1.4)	36 (1.7)
Did not receive Dose 3 within the predefined window[b]	2 (0.1)	4 (0.6)	6 (0.3)
Had other important protocol deviations on or prior to 7 days after Dose 3	12 (0.8)	3 (0.4)	15 (0.7)

Source: EUA 27034.636, eua-amendment-6m-4y-updated-efficacy.pdf, Page 23, Table 9.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Participants may have been excluded for more than one reason.
b. at least 60 days after Dose 2 for participants enrolled before protocol amendment 6 and 54-70 days for participants enrolled after protocol amendment 6

Vaccine administration timing: In the Dose 3 evaluable efficacy population, the median interval between Dose 2 and Dose 3 among participants 6-23 months of age was 13.4 weeks (range: 7.9 to 33.3 weeks) for BNT162b2 recipients and 13.9 weeks (range: 8.0 to 35.0 weeks) for placebo recipients.

Participants 2-4 years of age
The Phase 2/3 Dose 3 evaluable efficacy population without evidence of prior SARS-CoV-2 infection for participants 2-4 years of age included 554 BNT162b2 recipients and 224 placebo recipients and the median duration of blinded follow-up after Dose 3 was 2.4 months. As shown

in Table 2, a total of 1485 (63.2%) and 768 (65.5%) participants were excluded from the BNT162b2 and placebo groups, respectively, due to not receiving Dose 3 prior to unblinding.

Table 2. Disposition of Participants 2-4 Years, Phase 2/3 Efficacy Population, Study C4591007

Disposition, n (%)	BNT162b2 3 µg N=2349	Placebo N=1173	Total N=3522
Dose 1 all-available efficacy population	2349 (100.0)	1173 (100.0)	3522 (100.0)
Dose 3 all-available efficacy population	864 (36.8)	405 (34.5)	1269 (36.0)
Participants excluded from Dose 3 all-available efficacy population	1485 (63.2)	768 (65.5)	2253 (64.0)
Did not receive 3 vaccinations prior to unblinding	1485 (63.2)	768 (65.5)	2253 (64.0)
Dose 3 Evaluable efficacy population	820 (34.9)	383 (32.7)	1203 (34.2)
Participants without evidence of infection prior to 7 days after Dose 3	554 (23.6)	224 (19.1)	778 (22.1)
Participants excluded[a] from Dose 3 evaluable efficacy population	1529 (65.1)	790 (67.3)	2319 (65.8)
Did not receive all vaccinations as randomized	1485 (63.2)	768 (65.5)	2253 (64.0)
Did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	27 (1.1)	16 (1.4)	43 (1.2)
Did not receive Dose 3 within the predefined window[b]	24 (1.0)	15 (1.3)	39 (1.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	22 (0.9)	4 (0.3)	26 (0.7)

Source: EUA 27034.636, eua-amendment-6m-4y-updated-efficacy.pdf, Page 19, Table 7.
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Participants may have been excluded for more than one reason.
b. At least 60 days after Dose 2 for participants enrolled before Protocol Amendment 6 and 54-70 days for participants enrolled after Protocol Amendment 6.

Vaccine administration timing: In the Dose 3 evaluable efficacy population, the median interval between Dose 2 and Dose 3 among participants 2-4 years of age was 10.0 weeks (range: 7.9 to 34.1 weeks) for BNT162b2 recipients and 10.0 weeks (range: 8.0 to 31.1 weeks) for placebo recipients.

Demographics

Demographic characteristics for the Dose 3 evaluable efficacy population of participants 6 months through 4 years of age without evidence of prior SARS-CoV-2 infection up to 7 days post-Dose 3, are summarized in Table 3. Participants were predominately White and non-Hispanic. The median age was 16.0 months in vaccine recipients 6 through 23 months of age and the median age was 3.0 years in vaccine recipients 2 through 4 years of age. There were no notable imbalances in baseline characteristics between the treatment groups.

Table 3. Demographic and Baseline Characteristics of Participants 6 Months through 4 Years, Phase 2/3 Dose 3 Efficacy Population Without Evidence of Prior SARS-CoV-2 Infection[a] up to 7 Days Post Dose 3, Study C4591007

Characteristic	BNT162b2 3 µg N=873 n (%)	Placebo N=381 n (%)
Sex: Female	446 (51.1)	208 (54.6)
Sex: Male	427 (48.9)	173 (45.4)
Race: White	666 (76.3)	296 (77.7)
Race: Black or African American	30 (3.4)	12 (3.1)
Race: American Indian or Alaska Native	2 (0.2)	0
Race: Asian	87 (10.0)	38 (10.0)
Race: Native Hawaiian or Pacific Islander	0	1 (0.3)
Race: Other	88 (10.1)	34 (8.9)
Ethnicity: Hispanic or Latino	98 (11.2)	27 (7.1)
Ethnicity: Not Hispanic or Latino	774 (88.7)	354 (92.9)
Ethnicity: Not reported	1 (0.1)	0
Comorbidities[b]: Yes	76 (8.7)	37 (9.7)
Comorbidities[b]: No	797 (91.3)	344 (90.3)
Country: Poland	24 (2.7)	4 (1.0)
Country: United States	849 (97.3)	377 (99.0)

Source: EUA 27034.636, c4591007-interim-efficacy-tf-6m-4y.pdf, Page 21-22.
Abbreviations: NAAT=nucleic acid amplification test; N-binding=SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2;
N=number of randomized participants in the specified group (the denominator for the percentage calculations).
n=number of participants with the specified characteristic.
a. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.
b. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088.

Updated Descriptive Efficacy Analyses

Participants 6 months-4 years of age

Results of VE against protocol-defined COVID-19 based on the Dose 3 evaluable efficacy population without, and with or without, evidence of SARS-CoV-2 infection up to 7 days post-Dose 3 are shown in Table 4 and Table 5. Among participants 6 months through 4 years of age without evidence of infection, the estimated VE was 73.2% (95% CI: 43.8%, 87.6%). Similar VE was observed within each age group (6-23 months and 2-4 years) and among participants with or without evidence of infection. The median length of blinded follow-up post-Dose 3 was 1.7 months for participants 6-23 months of age and 2.1 months for participants 2-4 years of age in the Dose 3 evaluable efficacy population.

Table 4. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 3, Blinded Follow-Up Period, Participants 6 Months Through 4 Years, Without Evidence of Infection Prior to 7 Days After Dose 3, Dose 3 Evaluable Efficacy Population, C4591007

Age Group	BNT162b2 3 µg N=873 Cases, n1[a] Surveillance Time[b], (n2[c])	Placebo N=381 Cases, n1[a] Surveillance Time[b], (n2[c])	Vaccine Efficacy (%) (95% CI[d])
6 Months - 4 Years	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2-4 Years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6-23 Months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

N=total number of participants in the analysis population; n= number of participants at risk; py= person-years of follow-up.

Source: Adapted from EUA 27034.636, eua-amendment-6m-4y-updated-efficacy.pdf, Tables 11, Page 29.
a. n1=Number of participants meeting the endpoint definition.
b. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
c. n2=Number of participants at risk for the endpoint.
d. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 5. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Dose 3, Blinded Follow-Up Period, Participants 6 Months Through 4 Years, With and Without Evidence of Infection Prior to 7 Days After Dose 3, Dose 3 Evaluable Efficacy Population, C4591007

Age Group	BNT162b2 3 µg N=1294 Cases, n1[a] Surveillance Time[b], (n2[c])	Placebo N=612 Cases, n1[a] Surveillance Time[b], (n2[c])	Vaccine Efficacy (%) (95% CI[d])
6 Months - 4 Years	14 0.149 (981)	23 0.067 (459)	72.5 (44.3, 86.9)
2-4 Years	10 0.100 (639)	15 0.044 (286)	70.7 (30.3, 88.2)
6-23 Months	4 0.048 (342)	8 0.023 (173)	76.2 (11.1, 94.8)

N=total number of participants in the analysis population; n= number of participants at risk; py= person-years of follow-up.
Source: Adapted from EUA 27034.636, eua-amendment-6m-4y-updated-efficacy.pdf, Tables 12, Page 30.
a. n1=Number of participants meeting the endpoint definition.
b. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
c. n2=Number of participants at risk for the endpoint.
d. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

All post-Dose 3 cases occurred from February-June 2022, during circulation of the Omicron BA.1 and BA.2 variants in the US.

<u>Reviewer Comment:</u> Limitations to these updated vaccine efficacy results include the following:

- *These 3-dose vaccine efficacy analyses were conducted after immunobridging statistical criteria post-Dose 2 were not met and after multiple looks at corresponding vaccine efficacy following both the 2-dose and 3-dose series. Therefore, these results are exploratory in nature.*
- *The dosing intervals between Doses 2 and 3 were highly variable, as Dose 3 was introduced following unsatisfactory post-Dose 2 effectiveness and safety results via a protocol amendment, with a median interval of 13.6 weeks (range 8 to 35 weeks) among participants 6-23 months of age and 10 weeks (range 8 to 34 weeks) among participants 2-4 years of age in the Dose 3 evaluable efficacy population.*
- *Systematic unblinding which occurred before participants had the option for Dose 3 and voluntary unblinding and placebo crossover which occurred after participants had the option for Dose 3 both contributed to the limitations for interpreting these vaccine efficacy results because participants' decision to remain in the Dose 3 efficacy analysis populations may be different across the two treatment groups and the remaining subjects may not reflect the originally randomized population. Of note, a majority of the blinded surveillance time collected after 7 days post-Dose 3 were contributed by participants enrolled prior to the protocol amendment. Due to the relatively low proportion of participants receiving Dose 3 and contributing blinded follow-up afterwards, representativeness of the efficacy population in both treatment groups to the original randomized population is unknown.*

Severe COVID-19

One confirmed COVID-19 case which occurred 44 days after Dose 3 in a 14-month-old placebo recipient met the criteria for severe COVID-19 because of an increased heart rate (HR) of 172 beats per minute (bpm), in the context of fever. The participant reported symptoms of fever, rhinorrhea, sneezing and new or increased cough. Initial central lab COVID-19 testing was negative within 5 days of symptom onset; however, because of increased cough, repeat central lab testing was repeated 9 days after the first test and was positive. BioFire testing identified coinfection with human rhinovirus/enterovirus. Nine days later, the participant went to the emergency department (ED) after a generalized tonic-clonic seizure lasting approximately 5-10 minutes. Vital signs in the ED included a temperature of 38.4°C, HR 172 bpm, with the following symptoms noted: cough, runny nose and congestion; no diagnostic tests were performed, and the participant was discharged home the same day, after observation. All symptoms were reported as resolved 8 days after the ED visit. Because the participant had not returned back to baseline prior to the ED visit for febrile seizure, the investigator thought the fever could be attributable to COVID-19 illness.

No cases of multisystem inflammatory syndrome in children were reported through the June 17, 2022 data cutoff date.

The Sponsor's proposal to add vaccine efficacy data to the EUA Fact Sheets is acceptable.

FDA Review of Proposed Fact Sheet Revisions

Pfizer submitted EUA amendment 658 (EUA 27034.658) on September 10, 2022 to revise the Fact Sheets to add dizziness to the Post Authorization Experience Section 6.2 for Healthcare Providers Fact Sheets and to the side effects section of the Recipient Fact Sheet. Review of the Sponsor's safety data and VAERS data showed that dizziness is one of the most frequently reported adverse events following vaccination with the Pfizer-BioNTech COVID-19 Vaccines (monovalent and bivalent) in the post-authorization setting. Most reports were non-serious and were for females. The time to onset was frequently in close temporal proximity to vaccination, and dizziness occurred following both primary series and booster doses. Most events of dizziness were reported along with other reactogenic adverse events. Please see the CBER/OBPV/DPV review memorandum for further details.

The Sponsor's proposal to add dizziness to the EUA Fact Sheets is acceptable.

EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

References

1. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-8.