



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Biostatistics

## STATISTICAL REVIEW AND EVALUATION EUA AMENDMENT

**EUA/Supplement Number:** 27034 (Amendment 132)

**Product Name:** COVID-19 vaccine

**Authorized Use:** 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

**Sponsor:** Pfizer

**Date submitted:** April 09, 2021

**Statistical Branch:** Vaccines Evaluation Branch

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## 1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of February 26, 2021, has caused more than 113 million cases of COVID-19 and claimed the lives of more than 2.5 million people worldwide. In the United States, more than 28 million cases and 503,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an Emergency Use Authorization (EUA) for a COVID-19 vaccine after determining that certain statutory requirements are met.

On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. On April 9, 2021, the sponsor (Pfizer, on behalf of Pfizer and BioNTech) submitted an amendment to the EUA, requesting extension of the emergency use authorization to individuals 12 through 15 years of age (abbreviated 12-15 years). The EUA amendment request includes safety and effectiveness data from the ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech Vaccine in 2,260 participants 12-15 years of age. Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in participants 12-15 years of age with titers of young adults 16-25 years of age, in whom vaccine efficacy (VE) has been demonstrated. In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race, and sex. In the supplemental efficacy analysis, VE after 7 days post Dose 2 was 100%, (95% CI: 75.3, 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of 2 months of follow-up after the second dose suggest a favorable safety profile. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), and injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in up to 2.4% of 12-15-year-old BNT162b2 participants, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose compared to age-matched placebo participants. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. Two 12-15-year old BNT162b2 participants withdrew from the study due to an AE; one participant experienced fever (40.3°C) starting 1 day after Dose 1 and resolved 2 days later, and one participant experienced exacerbation of pre-existing anxiety and depression. No deaths were observed in this age group during this follow up period. Serious adverse events were uncommon (<0.5%) and represented medical events that occur in the general population at similar frequency as observed in the study. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to BNT162b2 vaccine.

Overall, the safety and effectiveness data support the issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

This memo was based on the joint clinical, statistical sections of EUA 27034.132 review memo; only contents relevant to statistical review were preserved.

## 2. Background

### 2.1 Authorized Vaccines and Therapies for COVID-19

Vaccines to prevent COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks. Pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which allows the FDA to authorize unapproved medical products for use in an emergency when certain criteria are met, the FDA has issued EUAs for three COVID-19 vaccines ([Table 1](#)). Of these, the two mRNA vaccines authorized in December 2020 have shown to be at least 90% effective in preventing COVID-19 in adults. However, no vaccine against COVID-19 has been authorized for use in children and adolescents under 16 years of age.

**Table 1. COVID-19 Vaccines Authorized for Emergency Use by the FDA**

Sponsor	Regimen	Indicated Population	Date of EUA
Pfizer	2 doses 3 weeks apart	Individuals ≥16 years of age	December 11, 2020
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. FDA subsequently issued EUAs for two monoclonal antibody combinations for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.

### 2.2 EUA Amendment Request for the Pfizer-BioNTech COVID-19 Vaccine

Pfizer, in partnership with BioNTech SE, has developed a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles. The Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is administered as a series of two 30-µg intramuscular injections spaced 21 days apart. The vaccine is supplied as a multi-dose vial containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for six 0.3 mL doses. The vaccine is preservative free.

Based on the protocol-specified final analysis of efficacy results from a Phase 2/3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants, the FDA issued an EUA for use of BNT162b2 to prevent COVID-19 in individuals 16 years of age and older on December 11, 2020. On April 9, 2021 Pfizer and BioNTech submitted a request to amend this EUA for the purpose of expanding the use of BNT162b2 to individuals 12 years of age and older. The request is accompanied by clinical trial data evaluating the safety and

effectiveness of the vaccine in 2,260 participants 12-15 years of age, which includes a total of 1,131 vaccine recipients, 58.3% of whom had  $\geq 2$  months of follow-up after Dose 2.

### 3. FDA Review of Clinical Safety and Effectiveness Data

#### 3.1 Overview of Clinical Studies

The EUA amendment request included data from one ongoing clinical study, summarized in [Table 2](#) below. Study C4591001 is a multi-center, multi-national Phase 1/2/3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study. Data from this study were used to support the existing EUA for individuals 16 years of age and older.<sup>1</sup> The focus of this EUA review is the data for participants 12-15 years of age and a comparison group of participants 16-25 years of age.

**Table 2: Study C4591001 in Participants 12 Through 15 and 16 Through 25 Years of Age**

Study Number/ Countries	Description	BNT162b2 (30 µg) N	Placebo (Saline) N	Study Status
C4591001 USA, Argentina, Brazil, Germany, South Africa, Turkey	Phase 1/2/3, randomized, placebo- controlled, observer- blind; to evaluate safety, immunogenicity and efficacy of COVID- 19 vaccine	Total: 3009 12-15 years: 1134 16-25 years: 1875	Total: 3043 12-15 years: 1130 16-25 years: 1913	Ongoing

N=Number of randomized participants as of March 13, 2021.

Study C4591001 began in April 2020 (first participant, first visit); participants 12-15 years of age: first participant, first visit was October 15, 2020 (implemented according to protocol amendment 7).

Source: Adapted from Tables A and D of C4591001-508-compliant-tables-12-15.

#### 3.2 Study C4591001

##### 3.2.1 Design

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. Adolescents were added to the protocol during Phase 3, following a review of safety data in young adult participants. This resulted in three age strata as follows: 12-15 years, 16-54 years, and 55 years and older.

The protocol-specified evaluation for vaccine effectiveness in participants 12-15 years of age was defined as an immunobridging evaluation comparing SARS-CoV-2 50% neutralizing antibody titers at 1 month after Dose 2 with those of young adults 16-25 years of age, in whom VE has been demonstrated.

##### Immunogenicity endpoint for adolescents 12 through 15 years of age

- GMR: the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the two age groups (12-15 years and 16-25 years) 1 month after completion of vaccination, in participants without serological or virological evidence of past SARS CoV-2 infection.
- Immunobridging would be demonstrated upon rejection of the null hypothesis: GMR of neutralizing antibody titers (adolescents to young adults)  $< 0.67$ -fold, i.e., the lower bound of the 95% CI for the GMR is  $> 0.67$ .

Supplementary to the immunobridging analysis, adolescents were followed for potential cases of COVID-19 to assess VE using the same methods as for participants 16 years of age and older. The primary efficacy endpoint of Study C4591001 was efficacy of the vaccine against laboratory-confirmed COVID-19 in participants without prior SARS-CoV-2 infection. A second efficacy endpoint included participants with and without prior SARS CoV-2 infection. COVID case definitions may be found in the review of the EUA for individuals 16 years of age and older.

Per protocol, since December 14, 2020, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo. Participants 12-15 years of age were all enrolled at sites in the U.S. and remain blinded to treatment assignment, except for a few participants elected to be unblinded when they turned 16 years of age so they could receive the vaccine under the EUA for individuals 16 years and older.

## Evaluation of safety

All participants 12-15 years of age recorded local reactions, systemic events, and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after the last dose, and serious AEs (SAEs) from Dose 1 to the data cut-off or participant's unblinding date (whichever was earlier), all which were recorded on the case report form. The cut-off date for this EUA amendment was March 13, 2021.

Potential COVID-19 illnesses and their sequelae were not reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

## Analysis populations

Population	Description
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 2 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 dose of vaccine. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.
Reactogenicity subset	All 12-15-year-old participants in the safety population plus the subset of the 16-25-year-old participants in the safety population who had e-diary data reported after vaccination.

Source: Adapted from the analysis population table in Section 9.3 of Protocol C4951001, Amendment 15 submitted in IND 19736.263.



Phase 3 clinical endpoints and analyses outlined in this review are provided for the following age groups:

- Adolescents 12-15 years of age: immunobridging, efficacy and safety
- Young adults 16-25 years of age: reference group for immunogenicity, solicited local reactions and systemic AEs, unsolicited AEs (within 30 minutes, non-serious through 30 days after each vaccination), and SAEs through 30 days after each vaccination
- Adults 16-55 years of age: supportive safety data (SAEs and adverse events of special interest (AESIs)) from larger group of adult participants with longer-term follow-up.

### 3.2.2 FDA Assessment of Phase 2/3 Follow-Up Duration for Participants 12 Through 15 Years of Age

Participants 12-15 years of age began enrollment into Phase 3 of Study C4591001 on October 15, 2020 (implemented with protocol amendment 7). As of the March 13, 2021 data cutoff for this EUA amendment, a total of 2,260 adolescents (1,131 in the BNT162b2 group and 1,129 in the placebo group) were enrolled and contributed to the safety population; 57.9% of participants had ≥2 months of follow-up after Dose 2 ([Table 3](#)).

**Table 3. Follow-up Duration After Dose 2, Participants 12 Through 15 Years of Age, Safety Population**

Length of Follow-up <sup>c</sup>	Vaccine Group (as Administered)		Total (N <sup>a</sup> =2260) n <sup>b</sup> (%)
	BNT162b2 (30 µg) (N <sup>a</sup> =1131) n <sup>b</sup> (%)	Placebo (N <sup>a</sup> =1129) n <sup>b</sup> (%)	
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.

<sup>a</sup> N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.

<sup>b</sup> n=number of subjects with the specified characteristic.

<sup>c</sup> Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

Safety comparator group: As of March 13, 2021, a total of 3,770 participants 16-25 years of age (1,867 in the BNT162b2 group and 1,903 in the placebo group) were enrolled and contributed to the safety population, of which 3,622 (96.1%) and 3,292 (87.3%) participants had ≥1 months and ≥2 month of follow-up, respectively, after Dose 2.

### 3.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in [Table 4](#) (immunogenicity populations), [Table 5](#) (efficacy populations) and [Table 6](#) (safety population). Within each age group, the percentages of participants who discontinued or were lost to follow-up were generally balanced.

For immunogenicity analyses, the sponsor planned to select a random sample of 280 participants in the BNT162b2 group for each of the two age groups as an immunogenicity subset for immunobridging. To maintain blinding of the laboratory personnel, 50 participants who had received placebo were randomly selected from each of the two age groups for serology testing. The population for the analysis of the immunogenicity endpoint (Dose 2 evaluable immunogenicity population) included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo

group). The majority of exclusions from the immunogenicity analysis population were due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2 (mostly as the result of limited supply of the qualified viral lot at the testing laboratory) and were generally balanced across age and vaccine groups.

**Table 4. Disposition of Participants 12 Through 15 and 16 Through 25 Years of Age, Immunogenicity Populations**

<b>Disposition</b>	<b>12-15 Years BNT162b2 n (%)</b>	<b>16-25 Years BNT162b2 n (%)</b>	<b>12-15 Years Placebo n (%)</b>	<b>16-25 Years Placebo n (%)</b>
Randomized <sup>a</sup>	280 (100.0)	280 (100.0)	50 (100.0)	50 (100.0)
Dose 2 all-available immunogenicity population	210 (75.0)	191 (68.2)	36 (72.0)	34 (68.0)
Participants without evidence of infection prior to 7 days after Dose 2	NA	NA	NA	NA
Participants excluded from Dose 2 all-available immunogenicity population	70 (25.0)	89 (31.8)	14 (28.0)	16 (32.0)
Reason for exclusion <sup>b</sup>				
Did not receive 2 vaccinations	1 (0.4)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Dose 2 evaluable immunogenicity population	209 (74.6)	186 (66.4)	36 (72.0)	32 (64.0)
Participants excluded from evaluable immunogenicity population	71 (25.4)	94 (33.6)	14 (28.0)	18 (36.0)
Reason for exclusion <sup>b</sup>				
Randomized but did not meet all eligibility criteria	0	0	0	0
Did not provide informed consent	0	0	0	0
Baseline SARS-CoV-2 status was positive or not known	NA	NA	NA	NA
Did not receive 2 doses of the vaccine to which they were randomly assigned	1 (0.4)	0	0	0
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.4)	2 (0.7)	0	2 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Did not have blood collection within 28-42 days after Dose 2	3 (1.1)	16 (5.7)	0	3 (6.0)
Had important protocol deviation(s) as determined by the clinician	0	0	0	1 (2.0)

Source: EUA 27034.132, c4591001-12-15-tables-figures.docx, Table B, page 1.

<sup>a</sup> These values are the denominators for the percentage calculations.

<sup>b</sup> Participants may have been excluded for more than 1 reason.

NA=not applicable

**Table 5. Disposition of Participants 12 Through 15 Years of Age, Efficacy Populations**

<b>Disposition</b>	<b>BNT162b2 n (%)</b>	<b>Placebo n (%)</b>	<b>Total n (%)</b>
Randomized <sup>a</sup>	1134 (100.0)	1130 (100.0)	2264 (100.0)
Dose 1 all-available efficacy population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Participants without evidence of infection before Dose 1	1028 (90.7)	1023 (90.5)	2051 (90.6)

<b>Disposition</b>	<b>BNT162b2 n (%)</b>	<b>Placebo n (%)</b>	<b>Total n (%)</b>
Participants excluded from Dose 1 all-available efficacy population	3 (0.3)	1 (0.1)	4 (0.2)
Reason for exclusion <sup>b</sup>			
Did not receive at least 1 vaccination	3 (0.3)	1 (0.1)	4 (0.2)
Dose 2 all-available efficacy population	1123 (99.0)	1117 (98.8)	2240 (98.9)
Participants without evidence of infection prior to 7 days after Dose 2	1008 (88.9)	983 (87.0)	1991 (87.9)
Participants excluded from Dose 2 all-available efficacy population	11 (1.0)	13 (1.2)	24 (1.1)
Reason for exclusion <sup>b</sup>			
Did not receive 2 vaccinations	10 (0.9)	13 (1.2)	23 (1.0)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Evaluable efficacy (7 days) population	1119 (98.7)	1110 (98.2)	2229 (98.5)
Subjects without evidence of infection prior to 7 days after Dose 2	1005 (88.6)	978 (86.5)	1983 (87.6)
Participants excluded from evaluable efficacy (7 days) population	15 (1.3)	20 (1.8)	35 (1.5)
Reason for exclusion <sup>b</sup>			
Randomized but did not meet all eligibility criteria	1 (0.1)	0	1 (0.0)
Did not provide informed consent	0	0	0
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-23 days after Dose 1)	14 (1.2)	19 (1.7)	33 (1.5)
Had other important protocol deviations on or prior to 7 days after Dose 2	0	2 (0.2)	2 (0.1)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table C, pages 2-3.

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.

<sup>a</sup> These values are the denominators for the percentage calculations.

<sup>b</sup> Participants may have been excluded for more than 1 reason.

**Table 6. Disposition of Participants 12 Through 15 and 16 Through 25 Years of Age, Safety Populations**

<b>Treatment Group</b>	<b>12-15 Years BNT162b2 n (%)</b>	<b>16-25 Years BNT162b2 n (%)</b>	<b>12-15 Years Placebo n (%)</b>	<b>16-25 Years Placebo n (%)</b>
Randomized (N) <sup>a</sup>	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Completed 1 dose	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Completed 2 doses	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Safety population	1131 (99.7)	1867 (99.5)	1129 (99.9)	1903 (95.9)
Reactogenicity subset	1131 (99.7)	537 (28.6)	1129 (99.9)	561 (29.3)
HIV-positive	0	1 (0.05)	0	0
Participants excluded from safety population	3 (0.26)	8 (0.42)	1 (0.08)	10 (0.52)
Reason for exclusion <sup>b</sup>				
Did not receive study vaccination	3 (0.26)	6 (0.32)	1 (0.08)	7 (0.36)
Unreliable data due to lack of PI oversight	0	2 (0.10)	0	3 (0.15)
Completed at least 2 months follow-up after Dose 2 <sup>c</sup>	660 (58.4)	1645 (88.1)	648 (57.4)	1647 (86.5)



<b>Treatment Group</b>	<b>12-15 Years BNT162b2 n (%)</b>	<b>16-25 Years BNT162b2 n (%)</b>	<b>12-15 Years Placebo n (%)</b>	<b>16-25 Years Placebo n (%)</b>
Completed 1-month after Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continued in the study up to 1-month after Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	7 (0.6)	12 (0.6)	10 (0.9)	36 (1.9)
Discontinued after Dose 2 and before 1-month post-Dose 2 visit	0	1 (0.1)	7 (0.6)	6 (0.3)
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria	3 (0.3)	4 (0.2)	10 (0.9)	26 (1.4)
Withdrawal by subject	0	6 (0.3)	1 (0.1)	1 (0.1)
Pregnancy	0	1 (0.1)	0	3 (0.2)
Adverse event	2 (0.2)	1 (0.1)	0	0
Physician decision	1 (0.1)	0	0	2 (0.1)
Protocol deviation	0	0	1 (0.1)	2 (0.1)
Lost to follow-up	0	0	0	1 (0.1)
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)
Withdrawn from study before 1-month post-Dose 2 visit	0	45 (2.4)	2 (0.2)	56 (2.9)
Withdrawn after Dose 1 and before Dose 2	0	25 (1.3)	1 (0.1)	34 (1.8)
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit	0	20 (1.1)	1 (0.1)	22 (1.2)
Reason for withdrawal				
Adverse event	0	0	0	1 (0.1)
Death	0	0	0	0
Withdrawal by subject	0	14 (0.7)	0	19 (1.0)
Lost to follow-up	0	29 (1.5)	0	32 (1.7)
Protocol deviation	0	0	1 (0.1)	1 (0.1)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.1)	0
Physician decision	0	0	0	1 (0.1)
Other	0	1 (0.1)	0	2 (0.1)

Source: EUA 27034.132, c4591001-12-15-tables-figures.docx, Table D, pages 3-4.

Note: The Human immunodeficiency virus (HIV)-positive subject included in this summary is not included in the analyses of the overall safety objectives. Safety data based on HIV-positive subjects were analyzed separately.

<sup>a</sup> N: denominator used for the percentage calculations.

<sup>b</sup> Participants may have been excluded for more than 1 reason.

<sup>c</sup> The numbers in this row are based on subjects who got dose 2 as administered. Duration of follow-up is based on blinded placebo-controlled follow-up period only.

PI=principal investigator

### **Statistical Reviewer Comment:**

Pfizer notified CBER on March 15, 2021 (IND 19736.242) that the laboratory had to halt sample testing due to insufficient supply of a critical assay reagent – the qualified viral lot, resulting in a smaller sample size available upon which to conduct the planned immunogenicity assessment. Upon a blinded review, numbers of subjects tested were roughly evenly split between the two age groups. Hence, CBER agreed with the sponsor's proposal to conduct the immunogenicity analysis only on subjects tested with the same viral reagent lot.

### 3.2.4 Demographics and Other Baseline Characteristics

The Dose 2 evaluable immunogenicity population included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo group) ([Table 7](#)).

The Dose 2 evaluable immunogenicity population of 12-15-year-olds who received the BNT162b2 included 49.3% females, 88.0% White, 7.7% African American, 2.4% Asian, and <2% from other racial groups; 10.5% of participants were Hispanic/Latino. The median age was 14 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 21.5% of participants. Geographically, all participants lived the U.S.

**Table 7. Demographics and Other Baseline Characteristics, Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population<sup>a</sup>**

<b>Characteristic</b>	<b>12-15 Years BNT162b2 (N=209) n (%)</b>	<b>16-25 Years BNT162b2 (N=186) n (%)</b>	<b>12-15 Years Placebo (N=36) n (%)</b>	<b>16-25 Years Placebo (N=32) n (%)</b>
Sex: Female	103 (49.3)	94 (50.5)	15 (41.7)	18 (56.3)
Sex: Male	106 (50.7)	92 (49.5)	21 (58.3)	14 (43.8)
Age: Mean years (SD)	13.5 (1.12)	20.6 (3.09)	13.4 (1.17)	20.3 (3.05)
Age: Median (years)	14.0	21.0	13.0	19.5
Race: American Indian or Alaska Native	1 (0.5)	3 (1.6)	0	1 (3.1)
Race: Asian	5 (2.4)	10 (5.4)	1 (2.8)	1 (3.1)
Race: Black or African American	16 (7.7)	15 (8.1)	3 (8.3)	2 (6.3)
Race: Native Hawaiian or other Pacific Islander	0	3 (1.6)	0	0
Race: White	184 (88.0)	147 (79.0)	31 (86.1)	28 (87.5)
Race: Multiracial	3 (1.4)	6 (3.2)	1 (2.8)	0
Race: Not reported	0	2 (1.1)	0	0
Race: Other	NA	NA	NA	NA
Ethnicity: Hispanic or Latino	22 (10.5)	31 (16.7)	2 (5.6)	7 (21.9)
Ethnicity: Not Hispanic or Latino	187 (89.5)	154 (82.8)	34 (94.4)	25 (78.1)
Ethnicity: Not reported	0	1 (0.5)	0	0
Obese <sup>b</sup> : Yes	24 (11.5)	43 (23.1)	3 (8.3)	4 (12.5)
Obese: No	185 (88.5)	143 (76.9)	33 (91.7)	28 (87.5)
Comorbidities <sup>c</sup> : Yes	45 (21.5)	56 (30.1)	7 (19.4)	9 (28.1)
Comorbidities: No	164 (78.5)	130 (69.9)	29 (80.6)	23 (71.9)
Baseline evidence of prior SARS-CoV-2 infection: Negative	194 (92.8)	178 (95.7)	33 (91.7)	31 (96.9)
Baseline evidence of prior SARS-CoV-2 infection: Positive	10 (4.8)	8 (4.3)	2 (5.6)	1 (3.1)
Baseline evidence of prior SARS-CoV-2 infection: Unknown	5 (2.4)	0	1 (2.8)	0
Region: North America	209 (100.0)	186 (100.0)	36 (100.0)	32 (100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table E, page 4-5.

<sup>a</sup> All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.

<sup>b</sup> Obese is defined as BMI  $\geq 30$  kg/m<sup>2</sup> ( $\geq 16$  years of age) or BMI  $\geq 95$ th percentile (12-15 years of age).

<sup>c</sup> Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis or obesity alone.

NA=not applicable

The Dose 1 all-available efficacy population of 12-15-year-olds (BNT 162b2 n=1,131, placebo n=1,129) were the same individuals as the 12-15-year-olds as in the safety population ([Table 8](#)).

Safety population: Among participants 12-15 years of age, the median age was 14 years and all participants lived in the U.S. Among participants 16-25 years of age, the median age was 18 years in the BNT162b2 group and 19 years in the placebo group; 81.2% and 77.4% participants, respectively, lived in the U.S.

**Table 8. Demographics and Other Baseline Characteristics, Participants 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset), Safety Population<sup>a</sup>**

<b>Characteristic</b>	<b>12-15 Years BNT162b2 (N=1131) n (%)</b>	<b>16-25 Years BNT162b2 (N=537) n (%)</b>	<b>12-15 Years Placebo (N=1129) n (%)</b>	<b>16-25 Years Placebo (N=561) n (%)</b>
Sex: Female	564 (49.9)	282 (52.5)	544 (48.2)	292 (52.0)
Sex: Male	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)
Age: Mean years (SD)	13.6 (1.11)	19.4 (3.26)	13.6 (1.11)	19.6 (3.33)
Age: Median (years)	14.0	18.0	14.0	19.0
Race: American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Race: Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Race: Black or African American	52 (4.6)	47 (8.8)	57 (5.0)	50 (8.9)
Race: Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Race: White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Race: Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Race: Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Race: Other	0	0	0	0
Ethnicity: Hispanic or Latino	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Ethnicity: Not Hispanic or Latino	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Ethnicity: Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Obese: Yes	143 (12.6)	80 (14.9)	128 (11.3)	101 (18.0)
Obese: No	988 (87.4)	80 (14.9)	1001 (88.7)	460 (82.0)
Comorbidities <sup>b</sup> : Yes	248 (21.9)	126 (23.5)	240 (21.3)	144 (25.7)
Comorbidities: No	883 (78.1)	411 (76.5)	889 (78.7)	417 (74.3)
Baseline evidence of prior SARS-CoV-2 infection: Negative	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Baseline evidence of prior SARS-CoV-2 infection: Positive	46 (4.1)	522 (93.0)	47 (4.2)	522 (93.0)
Baseline evidence of prior SARS-CoV-2 infection: Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)
Region: North America	1131 (100.0)	436 (81.2)	1129 (100.0)	434 (77.4)
Country: Argentina	0	20 (3.7)	0	28 (5.0)
Country: Brazil	0	24 (4.5)	0	19 (3.4)
Country: Germany	0	11 (2.0)	0	20 (3.6)
Country: South Africa	0	34 (6.3)	0	45 (8.0)

Characteristic	12-15 Years BNT162b2 (N=1131) n (%)	16-25 Years BNT162b2 (N=537) n (%)	12-15 Years Placebo (N=1129) n (%)	16-25 Years Placebo (N=561) n (%)
Country: Turkey	0	12 (2.2)	0	15 (2.7)

Sources: EUA 27034.132, eua-amend-12-15-years.pdf, Table 5, page 23 and c4591001-12-15-tables-figures.docx, Table P, page 7-9.

<sup>a</sup> All randomized participants who receive at least 1 dose of the study intervention.

<sup>b</sup> Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis - or obesity alone (BMI  $\geq 30$  kg/m<sup>2</sup> [ $\geq 16$  years of age] or BMI  $\geq 95$ th percentile [12-15 years of age]).<sup>b</sup> Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis or obesity alone (BMI  $\geq 30$  kg/m<sup>2</sup> [ $\geq 16$  years of age] or BMI  $\geq 95$ th percentile [12-15 years of age]).

### 3.2.5 Vaccine Effectiveness

#### Immunogenicity

The immune response to BNT162b2 in adolescents 12-15 years of age was noninferior to that observed in young adults 16-25 years of age, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2 in participants without prior evidence of SARS-CoV-2 infection. The geometric mean titer (GMT) ratio of adolescent to young adult neutralizing antibody titers was 1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5-fold non-inferiority criterion (i.e., lower bound of the 2-sided 95% CI for GMR  $> 0.67$ ).

**Table 9. Geometric Mean SARS-CoV-2 Neutralizing Titers (NT50) 1 Month After BNT162b2 Dose 2 in Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population**

Study Group	12-15 Years N=190 GMT (95% CI)	16-25 Years N=170 GMT (95% CI)	GMT Ratio [12-15 Years/ 16-25 Years] (95% CI)	Met Predefined Success Criterion <sup>a</sup>
BNT162b2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 85.

<sup>a</sup> Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

N=Number of participants with valid and determinate assay results for the specified assay at 1 month after Dose 2.

GMT=geometric mean titer

#### Statistical Reviewer Comment:

*I verified the immunobridging analysis based on GMTs.*

*One subject (10801055, 23 years old) was considered non-evaluable by the sponsor for the immunogenicity analysis due to a protocol deviation that may affect immune response (receiving another COVID vaccine). However, this deviation occurred on 12/21/2020, while the Month 1 post Dose 2 visit for this subject occurred on 10/7/2021. Therefore, the deviation should have no impact on the Month 1 post Dose 2 immunogenicity result. Nonetheless, this subject received placebo and excluding this subject had no impact on the immunobridging analyses.*

The GMR of SARS CoV-2 neutralizing titers one month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to make an interpretation.

**Table 10. Subgroup Analyses of Geometric Mean SARS-CoV-2 Neutralizing Titers (NT 50) One Month After BNT162b2 Dose 2 in Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 All-Available Immunogenicity Population**

<b>Subgroup</b>	<b>12-15 Years N, GMT (95% CI)</b>	<b>16-25 Years N, GMT (95% CI)</b>	<b>GMT Ratio [definition] (95% CI)</b>
Comorbid condition <sup>a</sup> : Yes	45, 1460.3 (1218.2, 1750.5)	56, 712.4 (546.0, 929.5)	2.05 (1.49, 2.82)
Comorbid condition: No	163, 1239.7 (1075.2, 1429.3)	134, 732.1 (641.6, 835.5)	1.69 (1.40, 2.05)
Obese: Yes	24, 1596.9 (1233.2, 2067.8)	43, 802.4 (613.5, 1049.4)	1.99 (1.33, 2.97)
Obese: No	184, 1284.4 (1097.1, 1420.5)	147, 705.4 (615.9, 807.9)	1.77 (1.47, 2.14)
Baseline SARS-CoV-2: Positive	10, 2342.2 (1308.7, 4191.8)	8, 1439.2 (727.1, 2848.7)	1.63 (0.72, 3.69)
Baseline SARS-CoV-2: Negative	193, 1240.9 (1098.7, 1401.5)	182, 704.7 (624.1, 795.9)	1.76 (1.48, 2.09)
Baseline SARS-CoV-2: Unknown	5, 1458.7 (479.2, 4440.9)	0, NE (NE, NE)	NE
Sex: Female	102, 1315.5 (1123.4, 1540.3)	98, 793.4 (665.9, 945.2)	1.66 (1.31, 2.09)
Sex: Male	106, 1255.2 (1051.3, 1498.5)	92, 661.0 (560.2, 780.0)	1.90 (1.49, 2.42)
Ethnicity: Hispanic or Latino	22, 1276.2 (917.9, 1774.4)	31, 662.4 (472.3, 928.9)	1.93 (1.20, 3.11)
Ethnicity: Not Hispanic or Latino	186, 1285.4 (1132.0, 1459.4)	158, 743.4 (652.9, 846.4)	1.73 (1.44, 2.07)
Ethnicity: Not reported	0, NE (NE, NE)	1,318.0 (NE, NE)	NE
Race: American Indian or Alaska Native	1, 908.0 (NE, NE)	3, 1130.7 (13.7, 93052.6)	0.80 (NE, NE)
Race: Asian	5, 1338.9 (625.6, 2865.8)	10, 649.6 (408.5, 1033.1)	2.06 (0.97, 4.38)
Race: Black or African American	16, 1377.3 (963.1, 1969.4)	15, 803.4 (409.7, 1575.8)	1.71 (0.82, 3.59)
Race: Native Hawaiian or Other Pacific Islander	0, NE (NE, NE)	4, 756.5 (184.9, 3094.1)	NE
Race: White	183, 1286.2 (1129.4, 1464.9)	150, 720.4 (633.2, 819.7)	1.79 (1.48, 2.15)
Race: Multiracial	3, 848.4 (224.8, 3202.1)	6, 741.5 (304.5, 1805.7)	1.14 (0.31, 4.16)
Race: Not reported	0, NE (NE, NE)	2, 486.7 (2.2, 108697.3)	NE

Source: EUA 27034.132, c4591001-12-15-tables-figures.docx, Table H, pages 6-8.

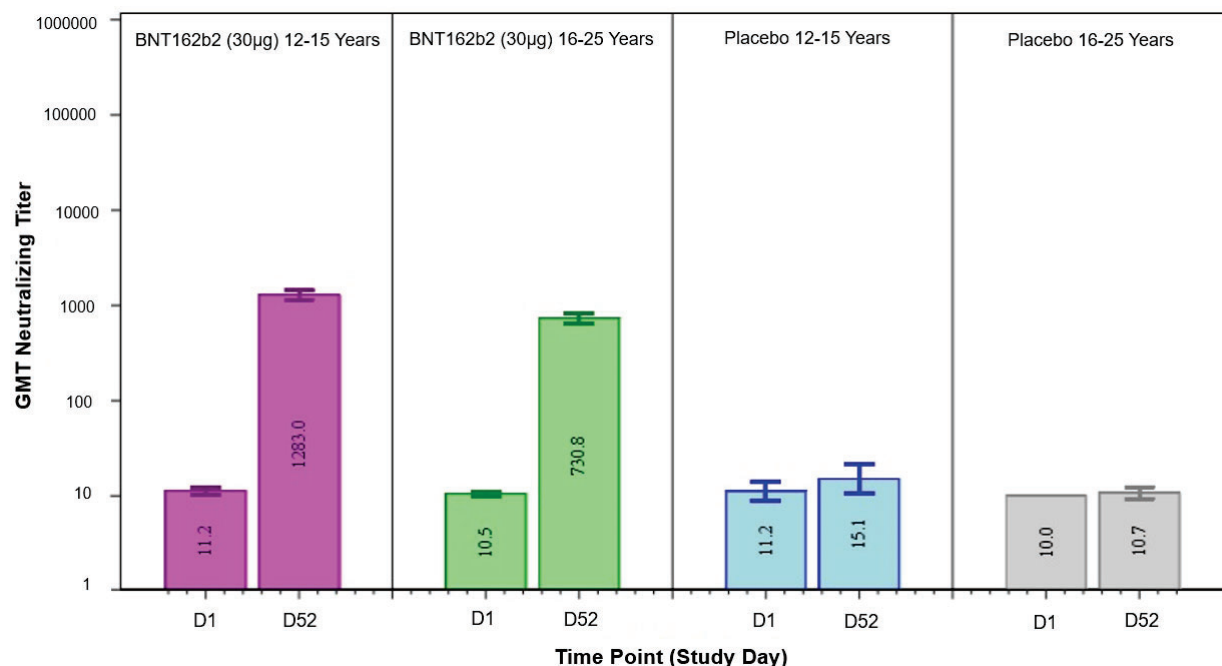
<sup>a</sup> Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis or obesity alone (BMI ≥30 kg/m<sup>2</sup> [≥16 years of age] or BMI ≥95th percentile [12-15 years of age]).

N=Number of subjects with valid and determinate assay results for the specified assay at 1 month after Dose 2.

GMT=geometric mean titer, NE=not estimable

The baseline SARS-CoV-2 neutralizing antibody GMTs obtained prior to vaccination were equally low in both age groups, with an observed increase in GMTs one month after Dose 2 in vaccine recipients ([Figure 1](#)).

**Figure 1. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population**



Source: EUA 27034, amendment 132, Figure 5; eua-amend-12-15-years.pdf, page 89.

D=day, GMT=geometric mean titer, NT50=50% neutralizing titer

Note: Number within each bar denotes geometric mean titer.

Seroresponse rates among participants without prior evidence of SARS-CoV-2 infection are displayed below in [Table 11](#). A  $\geq 4$ -fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2 was seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%).

**Table 11. Seroconversion Rates – NT50 – 1 Month After BNT162b2 Dose 2, Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population**

Study Group	12-15 Years N=143	16-25 Years N=124	Difference in Seroconversion Rates <sup>a</sup> (95% CI)
	n, SCR (%) (95% CI)	n, SCR (%) (95% CI)	
BNT162b2	140 (97.9) (94.0, 99.6)	124 (100.0) (97.1, 100.0)	-2.1 (-6.0, 0.9)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 86.

<sup>a</sup> Seroconversion is defined as achieving a  $\geq 4$ -fold rise from baseline (before vaccination).

N=number of participants with valid and determinate assay results for the specified assay both before vaccination and at 1 month after Dose 2.

n=number of participants with  $\geq 4$ -fold rise from before vaccination to 1 month after Dose 2

SCR=seroconversion rate

## Clinical Disease Endpoint Efficacy results

The protocol-specified final analysis of efficacy was completed with a data cutoff date of November 14, 2020. At that time, only 100 participants 12-15 years of age (49 in the BNT162b2 group and 51 in the placebo group) were enrolled in the study and there were no confirmed COVID-19 cases in this age group. Therefore, an additional analysis of VE in adolescents 12-15



years of age was conducted with all cases accrued during blinded follow-up to a data cutoff date of March 13, 2021.

For the first efficacy endpoint in participants 12-15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0%. The case split was 0 COVID-19 cases in the BNT162b2 group compared to 16 COVID-19 cases in the placebo group ([Table 12](#)). The 95% confidence interval for the VE was 75.3% to 100.0%.

**Table 12. Vaccine Efficacy, Participants 12 Through 15 Years of Age Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population**

Endpoint	BNT162b2 N <sup>a</sup> =1005 Cases n1 <sup>b</sup>	Placebo N <sup>a</sup> =978 Cases n1 <sup>b</sup>	Vaccine Efficacy % (95% CI) <sup>e</sup>
	Surveillance Time <sup>c</sup> (n2 <sup>d</sup> )	Surveillance Time <sup>c</sup> (n2 <sup>d</sup> )	
First COVID-19 occurrence from 7 days after Dose 2 in subjects without evidence of prior SARS-CoV-2 infection	0, 0.154 (1001)	16, 0.147 (972)	100.0 (75.3, 100.0)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 18, page 76.

<sup>a</sup> N=Number of participants in the specified group.

<sup>b</sup> n1=Number of participants meeting the endpoint definition.

<sup>c</sup> Total surveillance time in 1000 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 7 days after Dose 2 to the end of the surveillance period.

<sup>d</sup> n2=Number of participants at risk for the endpoint.

<sup>e</sup> Confidence interval (CI) for VE based on the Clopper-Pearson method adjusted to the surveillance time.

### Statistical Reviewer Comment:

*I verified the efficacy analysis.*

For the second efficacy endpoint in participants 12-15 year of age with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was also 100.0%, with 0 and 18 cases in the BNT162b2 and placebo groups, respectively. The 95% confidence interval for the VE was 78.1% to 100.0%.

### Subgroup analyses of vaccine efficacy

The demographics of the participants with confirmed COVID-19 cases contributing to the efficacy analysis are displayed below in [Table 13](#). All confirmed COVID-19 cases occurred in the placebo group in participants who had negative baseline SARS-CoV-2 status and who identified as White.

**Table 13. Demographic Characteristics, Participants 12 Through 15 Years of Age With Protocol-Defined COVID-19 (With or Without Evidence of Infection Prior to 7 Days After Dose 2)**

Characteristic	BNT162b2 N=0 n (%)	Placebo N=18 n (%)
Sex: Female	0	6 (33.3)
Sex: Male	0	12 (66.7)
Age at vaccination: Mean years (SD)	0	13.9 (1.16)
Age at vaccination: Median (years)	0	14.0
Race: American Indian or Alaska Native	0	0

Characteristic	BNT162b2 N=0 n (%)	Placebo N=18 n (%)
Race: Asian	0	0
Race: Black or African American	0	0
Race: Native Hawaiian or Other Pacific Islander	0	0
Race: White	0	18 (100.0)
Race: Multiracial	0	0
Ethnicity: Hispanic or Latino	0	5 (27.8)
Ethnicity: Not Hispanic or Latino	0	13 (72.2)
Comorbidities <sup>a</sup> : Yes	0	7 (38.9)
Comorbidities: No	0	11 (61.1)
Comorbidity: Obesity	0	4 (22.2)
Baseline SARS-CoV-2 Status: Negative	0	18 (100.0)

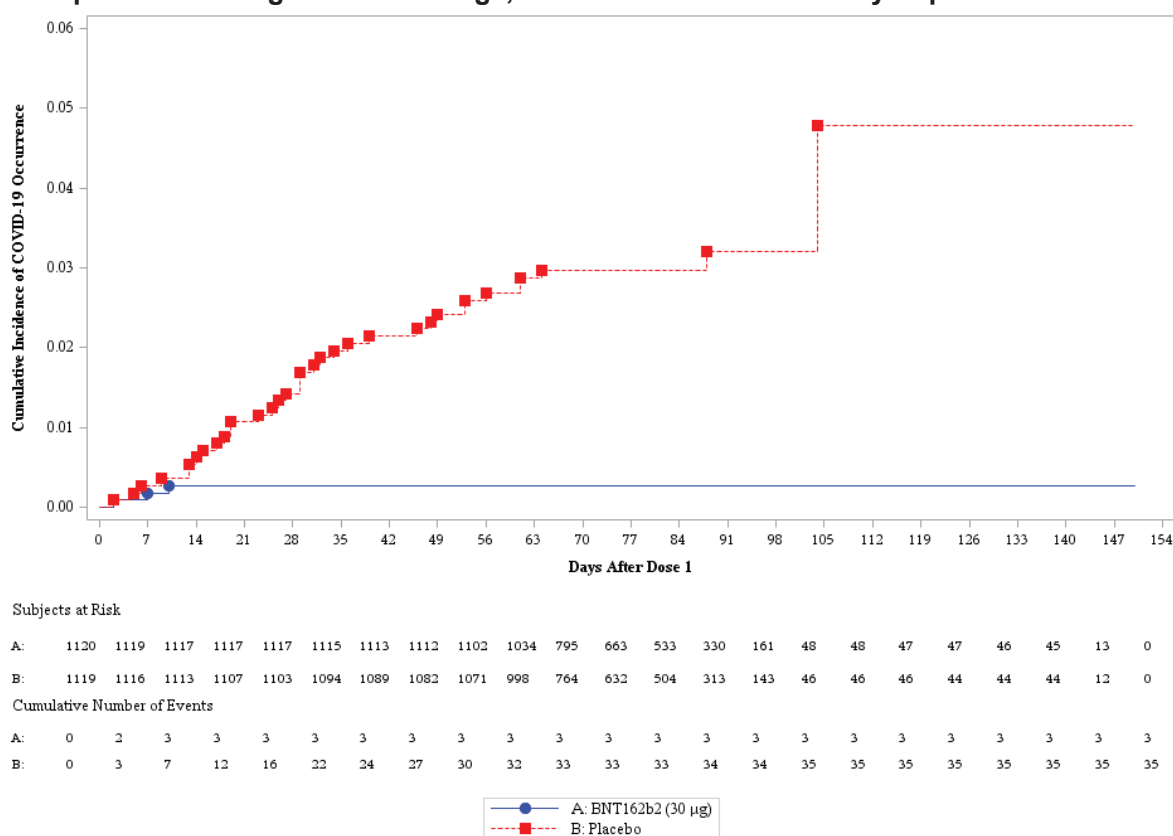
Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables L and M1, pages 12-14.

<sup>a</sup> Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis or obesity alone (BMI  $\geq 30$  kg/m<sup>2</sup> [ $\geq 16$  years of age] or BMI  $\geq 95$ th percentile [12-15 years of age]).

## Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1 (Figure 2), the curves diverge at Day 14, with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months following the second dose, there does not appear to be waning protection in the BNT162b2 group.

**Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population**



Source: EUA 27034, amendment 132; c4591001-508-compliant-tables-12-15.pdf, page 15.

## Severe COVID-19 cases

There were no reports of severe COVID-19 cases in participants 12-15 years of age.

## Additional efficacy analyses

Additional analyses of the efficacy endpoint were conducted to evaluate the all-available efficacy population of participants 12-15 years of age, regardless of evidence of prior infection from Dose 1 through 7 days after Dose 2 ([Table 14](#)).

**Table 14. Primary Efficacy Endpoint, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population**

Efficacy Endpoint	BNT162b2 N <sup>a</sup> =1131 Cases n <sup>1b</sup> Surveillance Time <sup>c</sup> (n <sup>2d</sup> )	Placebo N <sup>a</sup> =1129 Cases n <sup>1b</sup> Surveillance Time <sup>c</sup> (n <sup>2d</sup> )	Vaccine Efficacy % (95% CI) <sup>e</sup>
First COVID-19 occurrence after Dose 1	3 0.257 (1120)	35 0.250 (1119)	91.6 (73.5, 98.4)
After Dose 1 to before Dose 2	3	12	75.0 (7.4, 95.5)
Dose 2 to 7 days after Dose 2	0	5	100.0 (-9.1, 100.0)
≥7 Days after Dose 2	0	18	100.0 (77.3, 100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables N, pages 16.

<sup>a</sup> N=number of participants in the specified group.

<sup>b</sup> n1=number of participants meeting the endpoint definition.

<sup>c</sup> Total surveillance time in 1000 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.

<sup>d</sup> n2=number of participants at risk for the endpoint.

<sup>e</sup> Confidence interval (CI) for VE is derived based on the Clopper-Pearson method (adjusted for surveillance time for overall row).

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 91.6%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there may be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

## 3.2.6 Safety

### Overview of adverse events

[Table 15](#) summarizes adverse events in the safety population from Dose 1 through 1 month after Dose 2. All participants 12-15 years of age in the safety population were also enrolled in the reactogenicity subset.

**Table 15. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2 – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population**

Event	12-15 Years BNT162b2 N <sup>a</sup> =1131 n <sup>b</sup> (%)	16-25 Years BNT162b2 N <sup>a</sup> =536 n <sup>b</sup> (%)	12-15 Years Placebo N <sup>a</sup> =1129 n <sup>b</sup> (%)	16-25 Years Placebo N <sup>a</sup> =561 n <sup>b</sup> (%)
Any event	68 (6.0)	58 (10.8)	67 (5.9)	45 (8.0)
Related <sup>c</sup>	33 (2.9)	33 (6.2)	21 (1.9)	12 (2.1)
Severe	7 (0.6)	9 (1.7)	2 (0.2)	3 (0.5)

Event	12-15 Years BNT162b2 N <sup>a</sup> =1131 n <sup>b</sup> (%)	16-25 Years BNT162b2 N <sup>a</sup> =536 n <sup>b</sup> (%)	12-15 Years Placebo N <sup>a</sup> =1129 n <sup>b</sup> (%)	16-25 Years Placebo N <sup>a</sup> =561 n <sup>b</sup> (%)
Life-threatening	1 (0.1)	0	1 (0.1)	0
Any serious adverse event	4 (0.4)	2 (0.4)	1 (0.1)	2 (0.4)
Related <sup>c</sup>	0	0	0	0
Severe	2 (0.2)	2 (0.4)	0	1 (0.2)
Life-threatening	0	0	1 (0.1)	0
Any adverse event leading to withdrawal	2 (0.2)	1 (0.2)	0	2 (0.4)
Related <sup>c</sup>	1 (0.1)	1 (0.2)	0	0
Severe	1 (0.1)	1 (0.2)	0	0
Life-threatening	1 (0.1)	0	0	0
Death	0	0	0	0

Source: Table 6 of eua-amend-12-15-years submitted in EUA 27034.132.

<sup>a</sup> N: number of subjects in the specified group. This value is the denominator for the percentage calculations.

<sup>b</sup> N: Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.

<sup>c</sup> Assessed by the investigator as related to investigational product.

## Immediate AEs

**12-15-year-olds:** After Dose 1, immediate AEs were reported in none of the BNT162b2 participants and 4 (0.4%) placebo participants. After Dose 2, immediate AEs were reported in 2 (0.2%) BNT162b2 participants and 3 (0.3%) placebo participants.

**16-25-year-olds:** Among the BNT162b2 and placebo groups, the immediate AEs after Dose 1 and after Dose 2 were 0.4%-0.6%, and mostly due to injection site pain.

**Anaphylaxis:** There were no reports of anaphylaxis in the 12-15-year or 16-25-year age groups through the cutoff date of March 13, 2021.

## Solicited local reactions and systemic adverse events

### Solicited local reactions

For BNT162b2 participants in both age groups, injection site pain was the most frequent solicited local adverse reaction. The median onset for all solicited local reactions after either BNT162b2 dose was Day 1 (day of vaccination) to Day 3, and the median duration was 1-3 days. Local reactions occurred more frequently after Dose 1 than after Dose 2. Frequencies of severe local reactions were lower in participants 12-15 years of age than in those 16-25 years of age.

Among 12-15-year-olds, injection site reactions were more frequent in the BNT162b2 group than in the placebo group.

**Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset<sup>a</sup>**

Event	12-15	12-15	12-15	12-15	16-25	16-25
	Years	Years	Years	Years	Years	Years
	BNT162b2	Placebo	BNT162b2	Placebo	BNT162b2	BNT162b2
	Dose 1	Dose 1	Dose 2	Dose 2	Dose 1	Dose 2
	N=1127	N=1127	N=1097	N=1078	N=531	N=488
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain at the injection site <sup>b</sup>						
Any <sup>d</sup>	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)	443 (83.4)	378 (77.5)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)	204 (38.4)	202 (41.4)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)	227 (42.7)	169 (34.6)
Severe	11 (1.0)	0	7 (0.6)	0	12 (2.3)	7 (1.4)
Redness <sup>c</sup>						
Any <sup>d</sup>	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)	34 (6.4)	28 (5.7)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)	25 (4.7)	18 (3.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)	7 (1.3)	9 (1.8)
Severe	1 (0.1)	0	0	0	2 (0.4)	1 (0.2)
Swelling <sup>c</sup>						
Any <sup>d</sup>	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)	44 (8.3)	33 (6.8)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)	31 (5.8)	23 (4.7)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)	12 (2.3)	10 (2.0)
Severe	0	0	0	0	1 (0.2)	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables R and R.1, pages 18-19.

%,n/N. n=number of participants in the specified age group with the specified reaction. N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.

<sup>a</sup> All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.

<sup>b</sup> Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.

<sup>c</sup> Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.

<sup>d</sup> Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

### Solicited systemic AEs

Among BNT162b2 participants in both age groups, fatigue and headache were most common. The median onset of systemic events after either BNT162b2 dose occurred on Day 1 to Day 4, with resolution after a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days. Frequencies of severe systemic AEs, muscle pain, and joint pain were lower in participants 12-15 years of age than in those 16-25 years of age.

Within each age group, the frequency and severity of systemic AEs was higher after BNT162b2 Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar for both doses.

Among 12-15-year-olds, systemic AEs were more frequently reported in BNT162b2 participants than in the placebo group.

**Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset<sup>a</sup>**

<b>Event</b>	<b>12-15 Years BNT162b2 Dose 1 N=1127 n (%)</b>	<b>12-15 Years Placebo Dose 1 N=1127 n (%)</b>	<b>12-15 Years BNT162b2 Dose 2 N=1097 n (%)</b>	<b>12-15 Years Placebo Dose 2 N=1078 n (%)</b>	<b>16-25 Years BNT162b2 Dose 1 N=531 n (%)</b>	<b>16-25 Years BNT162b2 Dose 2 N=488 n (%)</b>
<b>Fever</b>						
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)	39 (7.3)	84 (17.2)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)	24 (4.5)	45 (9.2)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)	12 (2.3)	32 (6.6)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)	3 (0.6)	7 (1.4)
≥40.0°C	1 (0.1)	0	0	0	0	0
<b>Fatigue<sup>b</sup></b>						
Any <sup>e</sup>	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)	318 (59.9)	320 (65.6)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)	134 (25.2)	98 (20.1)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)	173 (32.6)	199 (40.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)	11 (2.1)	23 (4.7)
<b>Headache<sup>b</sup></b>						
Any <sup>e</sup>	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)	286 (53.9)	297 (60.9)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)	151 (28.4)	119 (24.4)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)	124 (23.4)	157 (32.2)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)	11 (2.1)	21 (4.3)
<b>Chills<sup>b</sup></b>						
Any <sup>e</sup>	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)	133 (25.0)	195 (40.0)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)	91 (17.1)	82 (16.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)	37 (7.0)	101 (20.7)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0	5 (0.9)	12 (2.5)
<b>Vomiting<sup>c</sup></b>						
Any <sup>e</sup>	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)	9 (1.7)	13 (2.7)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)	9 (1.7)	10 (2.0)
Moderate	0	2 (0.2)	4 (0.4)	1 (0.1)	0	3 (0.6)
Severe	1 (0.1)	0	0	0	0	0
<b>Diarrhea<sup>d</sup></b>						
Any <sup>e</sup>	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)	57 (10.7)	39 (8.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)	50 (9.4)	32 (6.6)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)	7 (1.3)	5 (1.0)
Severe	0	0	0	0	0	2 (0.4)
<b>New or worsened muscle pain<sup>a</sup></b>						
Any <sup>e</sup>	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)	143 (26.9)	199 (40.8)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)	67 (12.6)	93 (19.1)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)	71 (13.4)	97 (19.9)
Severe	2 (0.2)	0	6 (0.5)	2 (0.2)	5 (0.9)	9 (1.8)
<b>New or worsened joint pain<sup>a</sup></b>						
Any <sup>e</sup>	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)	70 (13.2)	107 (21.9)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)	38 (7.2)	49 (10.0)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)	29 (5.5)	54 (11.1)
Severe	1 (0.1)	0	4 (0.4)	0	3 (0.6)	4 (0.8)



Event	12-15	12-15	12-15	12-15	16-25	16-25
	Years	Years	Years	Years	Years	Years
	BNT162b2	Placebo	BNT162b2	Placebo	BNT162b2	BNT162b2
	Dose 1 N=1127 n (%)	Dose 1 N=1127 n (%)	Dose 2 N=1097 n (%)	Dose 2 N=1078 n (%)	Dose 1 N=531 n (%)	Dose 2 N=488 n (%)
Use of antipyretic or pain medication <sup>f</sup>	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)	167 (31.5)	223 (45.7)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables S and S.1, pages 20-22.

%;n/N. n=number of participants in the specified age group with the specified characteristic.

N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.

<sup>a</sup> All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.

<sup>b</sup> Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.

<sup>c</sup> Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.

<sup>d</sup> Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.

<sup>e</sup> Any systemic event: any fever  $\geq 38.0^{\circ}\text{C}$ , any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.

<sup>f</sup> Severity was not collected for use of antipyretic or pain medication.

## Non-serious unsolicited AEs

### Dose 1 through 1 month after Dose 2

#### *Lymphadenopathy*

Among 12-15-year-olds, lymphadenopathy was reported in 7 (0.6%) BNT162b2 participants and 1 (0.1%) placebo participant. AEs of lymphadenopathy were reported within 2-10 days after study intervention, located mainly in the arm/neck (axillary, cervical, supraclavicular lymph nodes), and assessed as related to the study product by the investigator. In approximately 50% of participants, lymphadenopathy resolved within 1-10 days; in the remaining participants, it was ongoing at the time of data cutoff. Three additional reports of lymphadenopathy (2 BNT162b2 and 1 placebo) were assessed as unrelated by the study investigator due to onset  $\geq 28$  days after Dose 2 in the 2 vaccine recipients and concurrent infectious mononucleosis in the placebo recipient. FDA agrees with the investigator's assessments.

#### *Reactogenicity*

Among the comparator group of 16-25-year-olds, higher frequencies of reported unsolicited non-serious adverse events in BNT162b2 participants compared to placebo participants were primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination and consistent with adverse reactions/events solicited among 16-25-year-old participants in the reactogenicity subset. For 12-15-year-old participants, the frequencies of similarly reported adverse reactions/events was lower, since all 12-15-year-olds were included in the reactogenicity subset.

### 1 month after Dose 2 to data cutoff date or participant's unblinding date (whichever is earlier)

*Bell's Palsy/Facial Paralysis/Facial Paresis:* No reports in participants 12-15 years or 16-25 years of age.

*12-15-year-olds:* There were no other notable patterns or numerical imbalances between treatment groups for specific categories (System Organ Class and Preferred Term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

## Serious adverse events

### Dose 1 through 1 month after Dose 2

From Dose 1 to 1 month after Dose 2, SAEs were reported in participants 12-15 years of age by 0.4% of BNT162b2 recipients and 0.1% of placebo recipients. All SAEs in BNT162b2 participants were considered unrelated to vaccination by the study investigator.

Among 12-15-year-olds, there were 5 SAEs (4 BNT162b2 participants, 1 placebo participant):

- BNT162b2

3 participants with prior histories of anxiety and depression were hospitalized for exacerbations of depression (18 days after Dose 1, 4 days after Dose 2, and 6 days after Dose 1, respectively), of which 1 reported concurrent anxiety exacerbation.

The fourth participant, a 12-year-old female, reported generalized neuralgia and had 3 emergency room visits beginning 1 day after Dose 2. She also reported 3 concurrent non-serious AEs (abdominal pain, vulvar abscess, gastritis) within the same week, and 6 days later developed constipation, and eventually diagnosed with functional abdominal pain. Following referral to a psychologist, her symptoms gradually improved but were ongoing at the time of the cutoff date. All SAEs in BNT162b2 participants were considered unrelated to vaccination by the study investigator.

- Placebo: a 13-year-old was hospitalized for appendicitis 19 days after Dose 2. The event resolved after 2 days and the participant continued in the study.

Among the comparator group of 16-25-year-olds, 6 BNT162b2 participants reported 7 SAEs: concurrent choledocholithiasis (1) and pancreatitis (1) in the same participant; abdominal pain (1), appendicitis (1), deep vein thrombosis (1), facial fracture (1), and osteochondritis (1). Four placebo participants reported 4 SAEs: appendicitis (1), inguinal hernia (1), flail chest (associated with a motor vehicle accident) (1), and incomplete spontaneous abortion (1). All SAEs in BNT162b2 participants were considered unrelated to vaccination by the study investigator. No further information was provided by the sponsor.

### 1 month after Dose 2 to data cutoff date or participant's unblinding date (whichever is earlier)

Between 1 month after Dose 2 and the cutoff date, there were 3 SAEs reported among 12-15-year-olds: 2 in BNT162b2 participants and 1 in a placebo participant. All SAEs in BNT162b2 participants were considered unrelated to vaccination by the study investigator.

- BNT162b2

- 12-year-old female participant with constipation was diagnosed with functional abdominal pain after an extensive work-up; she also developed generalized neuralgia beginning 1 day after Dose 2 (described above).
- 14-year-old female with prior history of anxiety and depression reported suicidal ideation 40 days after Dose 2, which was ongoing as of the data cutoff date.

- Placebo: a 15-year-old was hospitalized for appendicitis 63 days after the Dose 2 of placebo. Symptoms were ongoing as of the data cutoff date.

## Deaths

There were no deaths among participants 12-15 years or 16-25 years during the reporting period of Dose 1 to the data cutoff date.

## AEs leading to study withdrawal

Among 12-15-year-olds, 2 BNT162b2 participants and no placebo participants withdrew from the study due to an AE; one BNT162b2 participant experienced fever (T40.3°C) [non-serious AE] starting on Day 2 after the day of first BNT162b2 vaccination (Day 1) and resolved on Day 4, and the other BNT162b2 participant was hospitalized for exacerbation of pre-existing anxiety and depression (both SAEs; described above). The study investigator considered only the AE of fever to be related to vaccination.

## Pregnancies

During the reporting period, there were no pregnancies among 12-15-year-olds and 4 pregnancies (1 BNT162b2, 3 placebo) among 16-25-year-olds, all of which were ongoing at the time of data cut-off March 13, 2021.

## Supplemental Safety Data

Participants 16-55 years of age: Prior to unblinding and crossover of placebo participants, the phase 2/3 safety population consisted of 26,164 participants 16-55 years of age (13,069 BNT162b2, 13,095 placebo); 82.5% of BNT162b2 participants and 84.4% of placebo participants had 2 to <6 months of follow-up after Dose 2; 10.4% of BNT162b2 participants and 8.2% of placebo participants had ≥6 months of follow-up after Dose 2. [Table 18](#) summarizes adverse events in the safety population from Dose 1 to unblinding in participants 16-55 years of age.

**Table 18. Incidence rate of at Least 1 Adverse Event From Dose 1 to Unblinding Date – Phase 2/3 Subjects 16-55 Years of Age – Safety Population**

	BNT162b2 N <sup>a</sup> =12995, TE <sup>b</sup> =49.7			Placebo N <sup>a</sup> =13026, TE <sup>b</sup> =49.1		
Event	n <sup>c</sup> (%)	IR (/100 PY) <sup>d</sup>	95% CI <sup>e</sup>	n <sup>c</sup> (%)	IR (/100 PY) <sup>d</sup>	95% CI <sup>e</sup>
Any event	4396	88.4	(85.8, 91.0)	2136	43.5	(41.7, 45.4)
Related <sup>c</sup>	3484	70.0	(67.7, 72.4)	884	18.0	(16.8, 19.2)
Severe	193	3.9	(3.4, 4.5)	124	2.5	(2.1, 3.0)
Life-threatening	13	0.3	(0.1, 0.4)	20	0.4	(0.2, 0.6)
Any serious adverse event	103	2.1	(1.7, 2.5)	117	2.4	(2.0, 2.9)
Related <sup>c</sup>	3	0.1	(0.0, 0.2)	1	0.0	(0.0, 0.1)
Severe	56	1.1	(0.9, 1.5)	75	1.5	(1.2, 1.9)
Life-threatening	13	0.3	(0.1, 0.4)	20	0.4	(0.2, 0.6)
Any adverse event leading to withdrawal	22	0.4	(0.3, 0.7)	28	0.6	(0.4, 0.8)
Related <sup>c</sup>	9	0.2	(0.1, 0.3)	8	0.2	(0.1, 0.3)
Severe	5	0.1	(0.0, 0.2)	6	0.1	(0.0, 0.3)
Life-threatening	3	0.1	(0.0, 0.2)	5	0.1	(0.0, 0.2)

	BNT162b2 N <sup>a</sup> =12995, TE <sup>b</sup> =49.7			Placebo N <sup>a</sup> =13026, TE <sup>b</sup> =49.1		
Event	n <sup>c</sup> (%)	IR (/100 PY) <sup>d</sup>	95% CI <sup>e</sup>	n <sup>c</sup> (%)	IR (/100 PY) <sup>d</sup>	95% CI <sup>e</sup>
Death	3	0.1	(0.0, 0.2)	4	0.1	(0.0, 0.2)

Source: Table 17 of eua-amend-12-15-years submitted in EUA 27034.132.

<sup>a</sup> N: number of subjects in the specified group.

<sup>b</sup> TE = total exposure time in 100 person-years across all subjects in the specified group. Exposure time for a subject is the time from Dose 1 to the end of blinded follow-up. This value is the denominator for the incidence rate calculation.

<sup>c</sup> n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event," n = number of subjects reporting at least 1 occurrence of any event.

<sup>d</sup> Incidence rate (IR) is calculated as number of subjects reporting the event/total exposure time in 100 person-years (PY) across all subjects in the specified group.

<sup>e</sup> 2-sided CI based on Poisson distribution.

<sup>f</sup> Assessed by the investigator as related to investigational product.

#### 4. Overall Summary and Recommendation

Vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (in whom VE has been demonstrated). In the planned immunobridging analysis, the GMR of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). Immunogenicity outcomes were consistent across demographic subgroups. In the supplemental efficacy analysis, VE after 7 days post Dose 2 was 100%, (95% CI: 75.3, 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. Because the study was not designed to evaluate VE specifically in participants 12-15 years of age, we view these efficacy data as supportive of the immunogenicity results.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of 2 months of follow-up after the second dose suggest a favorable safety profile. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events that occurred in up to 2.4% of 12-15-year-old BNT162b2 participants were more frequent after Dose 2 than after Dose 1. Two 12-15-year old BNT162b2 participants withdrew from the study due to an AE. No deaths were observed in this age group during this follow up period. Serious adverse events were uncommon (<0.5%) and represented medical events that occur in the general population at similar frequency as observed in the study. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to BNT162b2 vaccine.

Overall, the safety and effectiveness data support the issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.